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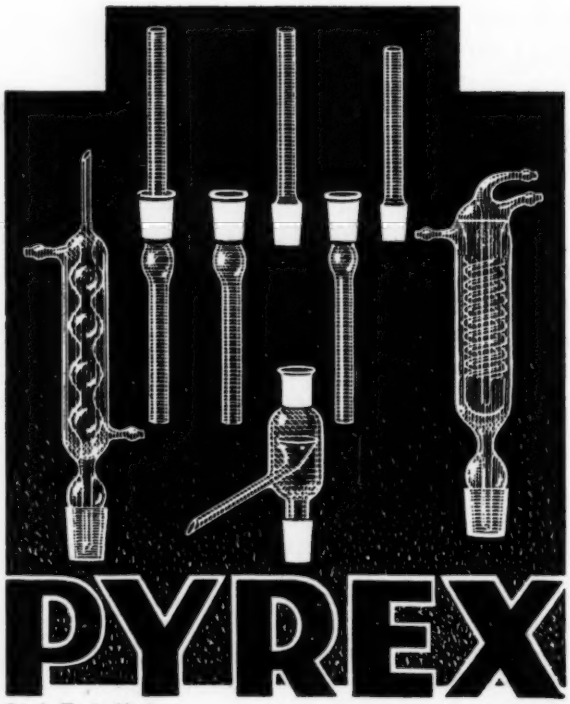

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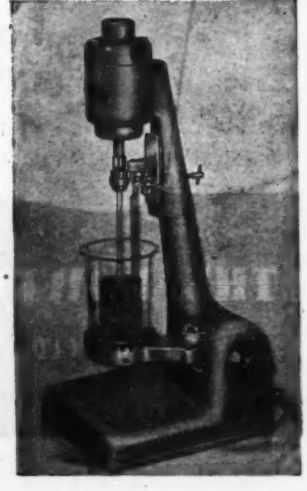

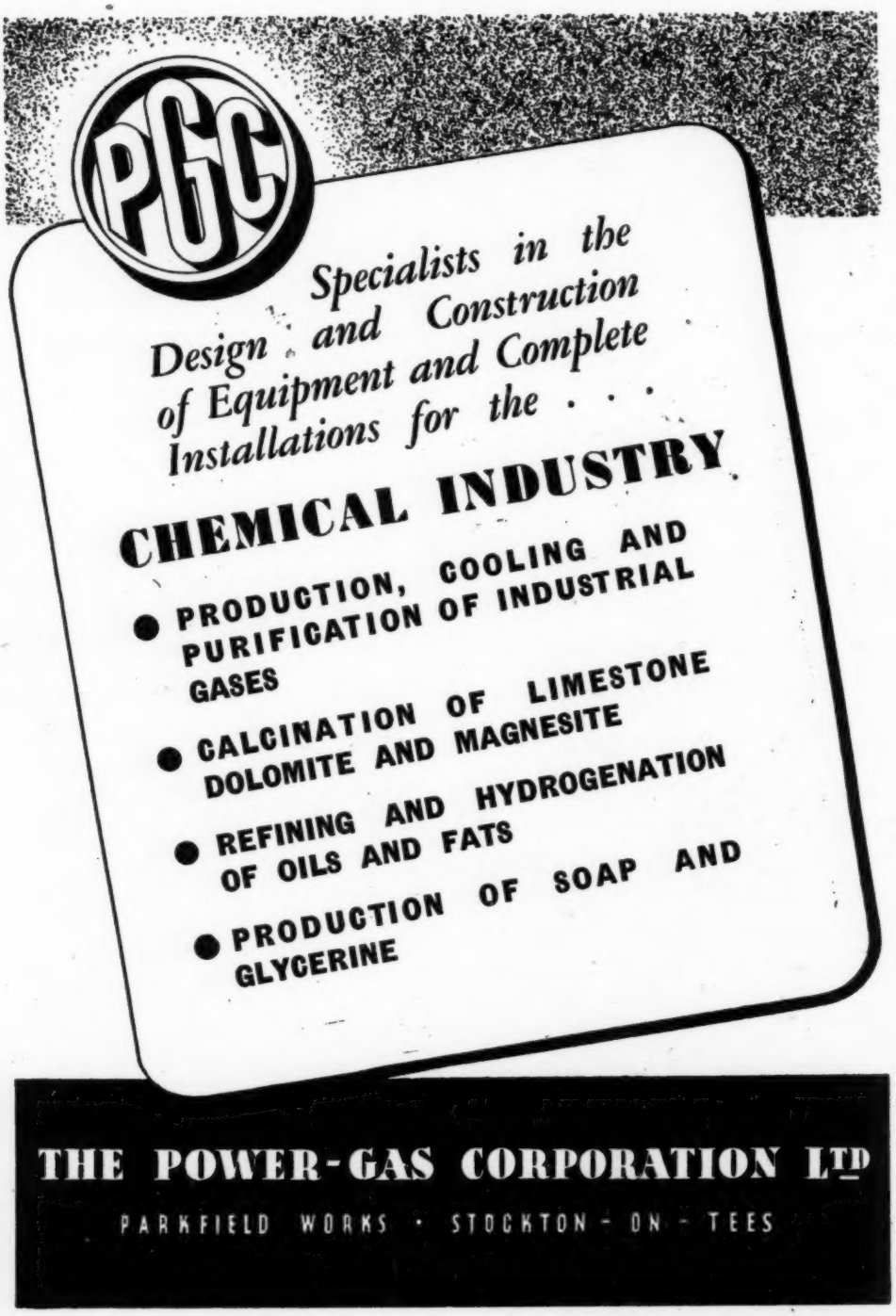
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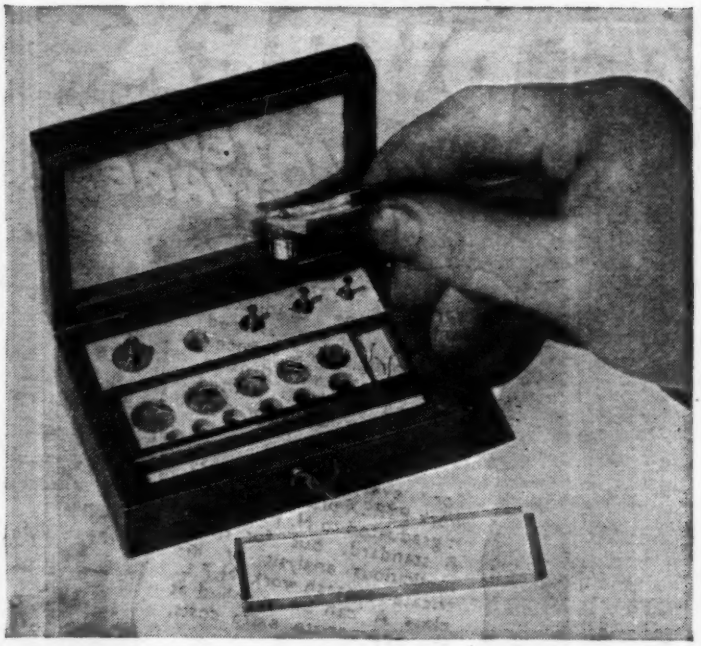

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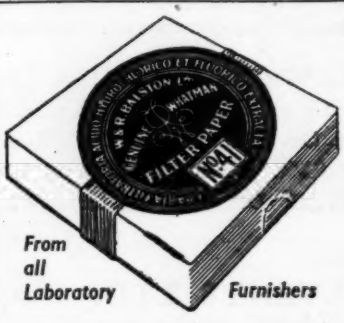

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GRACE CUMMING LEITCH.

1889—1942.

GRACE CUMMING LEITCH was born at Cupar, Fife, on July 14th, 1889, and died there on March 12th, 1942. From Bell Baxter School she proceeded to the University of St. Andrews, graduating M.A. in 1912 with honours in mathematics and natural philosophy; B.Sc. in 1913; and Ph.D. in chemistry in 1919. She was Assistant at St. Andrews and later became Lecturer in Chemistry (1920—1942) at King's College, Newcastle-upon-Tyne, University of Durham. From 1926 she served also as Sub-Warden of Easton Hall of Residence for women students. Her published researches in this *Journal* include papers with W. N. Haworth on lactose and melibiose (1918), maltose (1919), the biose of amygdalin (1922), and one paper on melezitose and turanose was published independently (1927); also papers with G. R. Clemo and others on lupin alkaloids (1928), lupanine (1931), phenyl- and pyridyl-glyoxalines (1938). Among scientific workers she had a wide acquaintance, fostered by her regular attendance at the annual British Association meetings. Few could have failed to appreciate her gaiety of spirit, warm enthusiasm and loyalty, her capacity for friendship, and her vigorous personality; for it was these qualities which commended her to her students and colleagues, by whom she will be greatly missed.

W. N. HAWORTH.

HERBERT MARSDEN.

1883—1943.

HERBERT MARSDEN died at The Lodge, Lockington, near Derby, on March 23rd, 1943, at the age of 60.

He was born at Church, Lancashire, passed through the Manchester Grammar School, and then went on to the Victoria University, Manchester. After having there taken an Honours degree in chemistry in 1905, he entered University College, Nottingham, in order to be trained as a research chemist. It was there that the writer made his acquaintance, and, after a very close association during two years, learnt to appreciate and admire not only his exceptional ability but also his personal qualities. His skilful manipulation and particular aptitude for research work were so notable that at the end of his first session the Council of the College awarded him a research scholarship, during the tenure of which he studied certain organic derivatives of silicon; a record of the results of his work was published in the *Transactions* for 1908 (p. 198) shortly after he had become a Fellow of the Society.

With strangers Marsden was quiet and rather reserved, but in the company of friends and fellow students he was genial and expansive, showing a lively interest in their affairs and, in fact, in all matters concerning the life of the College; when he left Nottingham in 1907 to become chemist to Messrs. E. Packard & Co., Ipswich, he had gained the respect and good wishes of all who had known him.

In 1918 he became chief chemist to Messrs. Genatosan Ltd., manufacturing chemists, a post which he held until his retirement in 1938.

Marsden had many interests apart from those of his profession: he was a man of deep religious feeling and during the last 30 years of his life did a great deal of voluntary work for the church as a lay reader. He was an accomplished pianist, an authority on ecclesiastical architecture (of which he had a collection of photographs, many his own work) and a keen and successful gardener.

He leaves a widow and one (married) daughter.

F. S. KIPPING.

JOSEPH WILLIAM MELLOR.*

1869—1938.

WITH the passing of Joseph William Mellor on May 24 science lost an outstanding worker. The clay industries of this country lost a great leader, a pioneer in clay technology, appreciated alike for his high endeavour, achievement, and astuteness.

Mellor was born at Huddersfield in 1869. When ten years old he was taken by his parents to New Zealand. During his youth he worked in a boot factory and took classes in the evenings at the Dunedin Technical School. At twenty-three he matriculated and a year later entered the University of Otago. After graduating and serving as a science lecturer at an agricultural college he was awarded an 1851 Exhibition which took him to the University of Manchester in 1899.

At Owens College, Mellor came under the influence of W. H. Perkin, jr., and H. B. Dixon. It is characteristic of his versatility that during this period at Manchester, from 1899 to 1904, he interested himself in problems of both inorganic and organic chemistry. Perkin suggested that he should synthesise and examine the α-alkyl derivatives of glutaric, adipic, and pimelic acids. His paper (*J. Chem. Soc.*, 1901, **79**, 1901) describes these syntheses and also records the dissociation constants of these acids. It was, however, the researches into the combination of hydrogen and chlorine, suggested by H. B. Dixon, which chiefly occupied his attention during his stay at Manchester. Prior to 1900, the union of these two gases had been studied by

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J. W. Draper, R. Bunsen and H. E. Roscoe, and E. Pringsheim. With his usual thoroughness, Mellor began his work by testing the conclusions of these workers. In Part 1 (*Proc. Chem. Soc.*, 1900, **16**, 221) he demonstrated the presence of oxygen as an impurity when hydrogen and chlorine are prepared by electrolysis. In Parts 2 and 3 (*J. Chem. Soc.*, 1901, **79**, 216) investigations on the solubility of chlorine in solutions of hydrochloric acid are recorded. With W. R. Anderson, he studied the Draper effect (*J. Chem. Soc.*, 1902, **81**, 414). The catalytic effect of water vapour on the reaction between the two gases had been investigated by H. B. Baker, who found that the dried, mixed gases only combined very slowly when exposed to sunlight. Baker's work was confirmed by Mellor, working in collaboration with E. J. Russell (*J. Chem. Soc.*, 1902, **81**, 1272). In Part 6 (*J. Chem. Soc.*, 1902, **81**, 1292) Mellor considered the period of induction associated with the combination of the gases. Previously this period had been adequately demonstrated by R. Bunsen and H. E. Roscoe. It had been explained as being due to the formation of an intermediate compound and its subsequent decomposition to give hydrochloric acid. E. Pringsheim had postulated a mechanism of the reaction based on the formation of Cl_2O as the intermediate compound. Mellor tested this hypothesis, found it untenable, and proceeded to indicate a mechanism based upon the formation of another intermediate compound. His later researches on this subject (*Proc. Chem. Soc.*, 1904, **20**, 53, 140, 196) were concerned with the effect of temperature on the period of induction and the activity acquired by chlorine on exposing this gas to light. By leading the electrolytic gases *via* separate tubes into the insolation vessel of the actinometer and exposing the chlorine on its way (*a*) to acetylene light, or (*b*) to the silent electric discharge, or (*c*) to the heat of a bunsen flame, he found that the period of induction was considerably reduced. Mellor's other publications during this period included a note on the filling of Bunsen's ice calorimeter (*J. phys. Chem.*, 1900, **4**, 135); a method of estimating cyanides and cyanates (*Z. anal. Chem.*, 1901, **40**, 17); and a paper (with L. Bradshaw) on the kinetics of sugar inversion (*Z. phys. Chem.*, 1904, **48**, 353).

On leaving Manchester, Mellor went to North Staffordshire, and, after a short period as science master at Newcastle (Staffs) High School, he began his long association with the ceramic industries on his appointment as lecturer in pottery manufacture in Stoke-on-Trent. He formed a great friendship with Bernard Moore, the eminent potter, whose collaboration over a period of thirty years he valued very highly. Mellor wrote more than a hundred papers on ceramics, published in the Transactions of the Ceramic Society, the first appearing in 1904; the last he completed two months before his death. These investigations covered a very wide field and included the plasticity of clays; the specific heat of firebricks at high temperatures; the action of heat on refractory materials; the fine grinding of ceramic materials; the constitution of the clay molecule; and the crazing, peeling, and durability of glazes. His early study of the constitution of the clay molecule led to a consideration of the effect of heat on clays. For this work he received a grant from the Royal Society. Presenting the paper reporting this work (*Trans. Eng. Ceram. Soc.*, 1911, **10**, 94) to the Ceramic Society, he wrote: " Perhaps some apology is needed for presenting a paper so purely chemical to our Society. But clay is the lifeblood of pottery, and it is difficult to live with clay day after day without trying to form some idea of its nature and character. To-day we may not know enough to see the practical bearing of this work but who dare predict what we shall see to-morrow? ". In a footnote he also wrote: " Mr. Bernard Moore kindly looked through the proofs and then drew our attention to an important practical bearing of our work on the industry." Actually, the results of this and other similar investigations form the basis of our modern conception of the firing of clay wares. Mellor was always intensely interested in glazes but left the publication of some of his important work on this aspect of ceramics until towards the end of his life. His papers on " The Crazing and Peeling of Glazes " and " The Durability of Pottery Frits, Glazes, Glasses, and Enamels in Service " appeared in 1935 and gained world-wide appreciation. Mellor's ceramic work reveals a freshness of experience and intimate contact with all he describes. His keen sense of analogy, his wit, and his lucid expression adorn his many writings.

As a teacher of ceramics, Mellor gained considerable reputation. In this capacity he rendered great service to the staple industry of Stoke-on-Trent. Starting under great difficulties, he saw the realisation of a major objective in the building of the North Staffordshire Technical College in 1914. Here he carried out his duties as Principal of the Pottery Department until his retirement in 1934. His own early struggles made him very appreciative of the difficulties of his evening students. Indeed, his humanity was the foundation of his success as a teacher.

He became associated with the work of the Ceramic Society about three years after its formation, becoming honorary secretary in 1905, a position he held until his death. He raised the status of the Society from a local association to that of an international institution. He extended its field to include refractory materials and clay building materials as well as pottery. The Society's present eminence is a lasting testimony to his high endeavour.

There is obviously a close relationship between certain problems of the pottery industry and some of the difficulties associated with firebrick manufacture. Clay is the basic material of both industries. Mellor realised that practically every industry employing high temperatures in manufacturing processes is limited in scope or in efficiency by the durability of refractory materials. He considered it his duty to make contact with both the manufacturers and users of refractory materials, and, in 1909, due in large measure to his initiative, the Refractories Committee of the Institution of Gas Engineers was formed. This was a pioneer association for the prosecution of research into the manufacture, properties, and durability of refractory materials. Its considerable development was an important factor in the establishment of the British Refractories Research

Association, in 1919, under the aegis of the Department of Scientific and Industrial Research. Mellor was appointed the first director of research of the Association, a position he held until 1937. He enlisted and retained the support of the manufacturers and users of refractory materials, carefully fostered the programme of research of the Association, and founded the Mellor Laboratories, the present headquarters. It is recognised that, in this work, he rendered a conspicuous service to his country.

It is no easy matter to assess, at short range, the work of any man with whom one has been closely associated for many years. In spite of this, it is clearly true to say that Mellor will be remembered for many years by reason of his monumental work, *A Comprehensive Treatise on Theoretical and Inorganic Chemistry*, in sixteen volumes, which he completed in 1937, after twenty years of courageous effort. He often said that, when writing the early volumes, he did not appreciate the extent of his task. It was in keeping with his character that having started this work he could not be deterred from completing it. As each volume appeared, he received unstinted, well-merited praise for this great service to his fellow scientists. To his few intimate associates, the completion of these volumes is a source of complete bewilderment. They know of his perfect indexing system, that he wrote every word and every reference, and that during the writing of the last four volumes he was a very sick man.

In 1901, while working in Manchester, Mellor conceived the idea of writing his first book, *Higher Mathematics for Students of Chemistry and Physics*. This ambitious work was the result of certain difficulties he experienced as a student endeavouring to follow the many developments in chemistry. The book had marked success, running into four editions and being reprinted in 1926. He often confessed that he obtained great pleasure from the writing of *Chemical Statics and Dynamics*, which appeared in 1904. His *Treatise on Quantitative Inorganic Chemistry*, which first appeared in 1912, is a recognised authoritative work on silicate analysis. Finally, his exceedingly popular *Modern Inorganic Chemistry*, a book of unique individuality, had a remarkable vogue in the whole of the English-speaking world. He certainly combined great scientific attainments with a singular literary ability. His work was recognised by many bodies. A number of foreign societies, particularly including the American Ceramic Society, made him an honorary member. He was elected a fellow of the Royal Society in 1927. In the Coronation Honours of 1937 he received the C.B.E.

Mellor had a very happy life. He looked forward to his work and to his leisure. As a youth, endowed with considerable physical strength, he enjoyed a good reputation as a swimmer. In later life, he played an enthusiastic game of bowls. He was a highly accomplished chess player. His sense of humour, combined with his ability as a cartoonist, delighted his many friends. He had a vivid appreciation of loyalty and friendship. To those who knew him, his supreme loyalty was, indeed, his greatest attribute.

A. T. Green.

COLIN RICHARD MORRISON-JONES.

1914—1942.

Colin Richard Morrison-Jones was killed in action in the Middle East in July, 1942, in his twenty-ninth year.

He was born on August 3rd, 1914, and educated at Merton Court, Sidcup, Cranleigh School, and the Royal College of Science. He graduated with Honours in Chemistry in 1935, and gained the A.R.C.S. the same year; afterwards he entered the research school of Professor J. F. Thorpe in Organic Chemistry. In the research laboratory he soon found his feet and became greatly interested in high-vacuum distillation processes, which he applied to the isolation of the individual polymers contained in thermally-treated vegetable oil esters; ultimately he shared in demonstrating the manner of thermal polymerisation characteristic of a conjugated diene ester, for which work he was awarded the degree of Ph.D.

In 1937 he became research assistant to the Rubber Growers' Association, and in this capacity did fruitful work in investigating the chemical reactivity of rubber. A year later he joined the research staff of the Anglo-Iranian Oil Company. Early in 1939 he became a member of the London Volunteer Fire Brigade and at the outbreak of war was called up for full-time service with this body. His work as a qualified fireman, however, was soon interrupted by a more urgent demand for his services as a chemist; fire-fighting then became a part-time occupation. In the stirring days of the early autumn of 1940 neither chemistry nor fire-fighting could hold him any longer, and after repeated applications he succeeded in getting released for service with the Royal Air Force. He trained as a fighter pilot in England and Canada and became in turn Sergeant-Pilot and Pilot Officer. After some service with a fighter squadron in Great Britain he was transferred abroad, arriving in time to fly a Hurricane in the defence of Malta during the great German attack on the island in the autumn of 1941. The next year he joined a fighter squadron in Libya, where he took part in the withdrawal to El Alamein. On July 24th, 1942, he was reported missing, and was later found to have been killed in action. He rests at El Dab'a.

Morrison-Jones hid high ability and a courageous spirit behind a shy and unassuming manner. Only on long acquaintance did the strength of purpose behind his quiet friendliness become apparent. His death came before he had reached the height of his powers, but not before he had been able to render notable and most gallant service to his country.

E. H. Farmer.

90. *The Preparation and Therapeutic Properties of Certain Acridine Derivatives. Part IV. 5-Methylacridines, Further 5-Styrylacridines and their Quaternary Salts.*

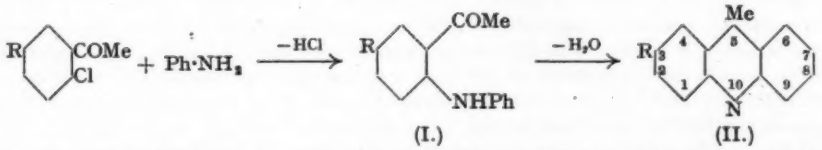
By W. Sharp, (Miss) M. M. J. Sutherland, and F. J. Wilson.

[With a Note on Antiseptic and Trypanocidal Action by C. H. Browning and (Miss) K. M. Calver.*]

This paper deals chiefly with those 5-styrylacridines containing amino-groups in both the styryl and the acridine portion of the molecule, together with certain amino-5-methylacridines. The therapeutic properties of these compounds, their quaternary salts, and the compounds described in Part III are now reported.

In Part III (this vol., p. 5) we described 5-styrylacridines and their quaternary salts containing substituents, amino- or dimethylamino-groups, in the styryl portion only. In view of the known effects of amino-groups in the acridine portion, we decided to introduce such groups into 5-methylacridine itself and into the 5-styryl derivatives, and to enhance the activity of such compounds by conversion into quaternary salts.

Jensen and Rethwisch (*J. Amer. Chem. Soc.*, 1928, **50**, 1144) prepared 4-nitro-2-acetyldiphenylamine (I, R = NO_2) from 2-chloro-5-nitroacetophenone and aniline and thence by ring closure 3-nitro-5-methylacridine (II, R = NO_2):



(I.) (II.)

This reaction, which we have improved, seemed to offer good possibilities, since substituted anilines could be used so that one ring would contain a nitro-group or, after reduction, an amino-group in position 3 and another substituent, such as an amino-group, would be present in the other ring. Albert and Linnell showed (J., 1938, 22) that an amino-group in position 3 results in a compound only slightly less active and much less toxic than one with the amino-group in position 2, which causes marked antiseptic properties.

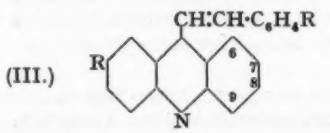
In preparing (II, R = NO_2) intermediate isolation of the diphenylamine derivative was necessary, direct condensation of the ketone with aniline to an acridine derivative proving unsuitable (compare Ullmann and Ernst, *Ber.*, 1906, **39**, 298). The intermediate diphenylamine derivatives, such as (I), do not fluoresce, but the acridine derivatives, such as (II), fluoresce in chloroform or benzene solution in ultra-violet light.

[1] Reduction of 3-nitro-5-methylacridine with stannous chloride and hydrochloric acid gave 3-amino-5-methylacridine (II, R = NH_2), which was converted into the crystalline stable *acetyl* derivative (II, R = NHAc), and then through the *metho*-p-*toluenesulphonate* (II, R = NHAc, + $C_6H_4Me{\cdot}SO_3Me$) into *3-amino-5-methylacridine methochloride*. An ethereal solution of 3-amino-5-methylacridine showed bright green fluorescence in daylight, a phenomenon not exhibited by the corresponding nitro- or acetamido-compound, which, however, gave a bright green fluorescence in glacial acetic acid in daylight. These characteristics have been observed generally with the amino- and acetamido-compounds described in this paper.

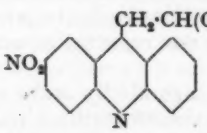
Jensen and Rethwisch state that the first stage of the reaction between 2-chloro-5-nitroacetophenone and *o*- or *p*-nitroaniline occurs, but give no details. We found, however, that, whereas the reaction with *o*-, *m*- or *p*-nitroaniline gave tarry products only, reaction ensued smoothly with *p*-aminoacetanilide, giving ultimately *3-nitro-7-amino-5-methylacridine*, the acetyl group being removed by hydrolysis during the working up. On reduction this gave 3 : 7-diamino-5-methylacridine, which was converted into the *diacetyl* derivative; the latter was converted through the metho-*p*-toluenesulphonate into 3 : *7-diamino-5-methylacridine methochloride* (II; R = NH_2, NH_2 at 7, + MeCl). A reaction between 2-chloro-5-nitroacetophenone and *m*-aminoacetanilide was also carried out, but ambiguity as to orientation arises in this case. The reaction proceeded similarly, giving ultimately probably 3-nitro-6 (or 8)-amino-5-methylacridine (or both); this on reduction yielded 3 : 6 (or 3 : 8)-diamino-5-methylacridine (or both), which, being only moderately antiseptic, was not further investigated.

2-Chloro-5-nitroacetophenone reacted with *p*-toluidine as with aniline; the resulting *3-nitro-5 : 7-dimethylacridine* (II; R = NO_2, Me at 7) on reduction gave 3-amino-5 : 7-dimethylacridine, which was converted through the *acetyl* derivative into *3-amino-5 : 7-dimethylacridine methochloride* (II; R = NH_2, Me at 7, + MeCl).

The condensation of 3-nitro-5-methylacridine with nitrobenzaldehydes was next attempted so as to obtain 5-nitrostyryl derivatives of type (III, R = NO_2) and thence by reduction diamino-compounds. When 3-



(III.)



(IV.)

* Working with the support of the Medical Research Council at the Bacteriology and Pathology Department of the University and Western Infirmary, Glasgow.

nitro-5-methylacridine was heated with *o*- or *m*-nitrobenzaldehyde alone, there resulted α-(o-*nitrophenyl*)-β-5-(3-*nitroacridyl*)*ethanol* or α-(m-*nitrophenyl*)-β-5-(3-*nitroacridyl*)*ethanol* (IV), which compounds, in view of previous experience, were not further investigated, especially as the *p*-aminostyrylacridine, on analogy with the *p*-aminostyrylquinolines, might be expected to be of more therapeutic interest. Heated in acetic anhydride solution, 3-nitro-5-methylacridine and *p*-nitrobenzaldehyde gave 3-*nitro*-5-p-*nitrostyrylacridine* (III, R = NO_2), which was converted by reduction into 3-amino-5-*p*-aminostyrylacridine, and thence through the *diacetyl* derivative into 3-*amino*-5-p-*aminostyrylacridine methochloride*. In precisely the same way, *p*-nitrobenzaldehyde and 3-nitro-5 : 7-dimethylacridine gave 3-*nitro*-5-p-*nitrostyryl*-7-*methylacridine*, 3-amino-5-*p*-aminostyryl-7-methylacridine, the *diacetyl* derivative, and finally 3-*amino*-5-p-*aminostyryl*-7-*methylacridine methochloride* (III; R = NH_2, Me at 7, + MeCl).

The *acetyl* derivative of 3-nitro-7-amino-5-methylacridine, on heating with *p*-nitrobenzaldehyde in acetic anhydride, gave 3-*nitro*-7-*acetamido*-5-p-*nitrostyrylacridine*, which on reduction and hydrolysis gave 3 : 7-diamino-5-*p*-aminostyrylacridine. This was converted through the *triacetyl* derivative into 3 : 7-*diamino*-5-p-*aminostyrylacridine methochloride* (III; R = NH_2, NH_2 at 7, + MeCl).

Antiseptic and Trypanocidal Action. [By C. H. BROWNING and K. M. CALVER].—The results of the examination of the compounds described in Part III and in the present paper are summarised below.

Biological properties were investigated by methods previously described (*Brit. J. Exp. Path.*, 1921, **2**, 95; *Proc. Roy. Soc.*, 1929, *B*, **105**, 99). The compounds in (*A*) and (*B*) were tested as hydrochlorides; those in (*C*), being already methochlorides, were water-soluble.

(*A*) 5-*Methylacridines*. 5-Methylacridine, owing to its limited solubility, could not be examined satisfactorily for antiseptic properties; the introduction of an amino-group in position 3 yielded a substance slightly antiseptic against staphylococcus in dilute peptone water (on account of poor solubility, however, the compound was partly dispersed). 3 : 7-Diamino-5-methylacridine was more antispetic, both staphylococcus and *B. coli* being sterilised by a concentration of 1 : 10,000—1 : 20,000. The increased antiseptic properties were lost, however, when the 7-position was occupied by a methyl group instead of an amino-group. Of the amino-5-methylacridines examined, the one showing strong antiseptic properties approaching those of acriflavine and proflavine was 3 : 6 (*or* 3 : 8)-diamino-5-methylacridine; the increase in antiseptic properties indicates that it probably contains the 3 : 8-derivative (see also Albert, Francis, Garrod, and Linnell, *Brit. J. Exp. Path.*, 1938, **19**, 41). None of these substances showed trypanocidal action, and none showed marked toxicity for mice on subcutaneous injection, a dose of 5 mg. of each being tolerated by a 20-g. mouse.

(*B*) 5-*Aminostyrylacridines*. 5-*p*-Amino-, -*m*-amino-, and -*p*-dimethylamino-styrylacridines all showed poor antiseptic properties, a concentration of 1 : 10,000 having no action and the position of and substitution in the amino-group apparently having no marked effect. Trypanocidal activity was not developed in any of these compounds and they were as little toxic as those above-named.

Combinations of these two structures, namely, an amino-group in the styryl part and amino-groups in the acridine part, again showed little or no antiseptic properties. Comparison of 3 : 7-diamino-5-*p*-aminostyrylacridine with 3 : 7-diamino-5-methylacridine indicates that the *p*-aminostyryl group in position 5 depresses antiseptic action compared with the methyl group in the same position, even allowing for the relative insolubility of the former in both peptone water and serum. Also the substances were little toxic (10 mg. being tolerated by a 20-g. mouse) and showed no trypanocidal activity.

(*C*) *Influence of quaternary salt formation.* (a) *On* 5-*methylacridine derivatives*. 5-Methylacridine methochloride had considerable antiseptic action, especially for staphylococcus in peptone water (sterilisation occurring at a dilution of 1 : 40,000); although little toxic for the mouse, a dose of 5 mg. had no trypanocidal action.

3-Amino-5-methylacridine methochloride showed marked increase in antiseptic properties as compared with both 3-amino-5-methylacridine hydrochloride and 5-methylacridine methochloride, but no trypanocidal activity. 3 : 7-Diamino-5-methylacridine methochloride also showed increase in antiseptic properties (cf. 3 : 7-diamino-5-methylacridine) and trypanocidal activity appeared. Replacement of the 7-amino-group by methyl did not notably affect antiseptic properties, but the trypanocidal action disappeared, although toxicity was higher in the case of 3 : 7-diamino-5-methylacridine methochloride—maximum tolerated dose, 2 mg. for a 20-g. mouse—whereas with 3-amino-5-methylacridine methochloride and 3-amino-5 : 7-dimethylacridine methochloride 4 mg. were borne.

(b) *On* 5-*styryl compounds*. 5-*p*-Aminostyrylacridine methochloride showed increase in antiseptic properties as compared with 5-*p*-aminostyrylacridine hydrochloride, but this was very little evident in the case of the *m*-amino-derivative. There was, however, an increase, especially for staphylococcus in peptone water, in the case of 5-*p*-dimethylaminostyrylacridine methochloride. 5-*p*-Aminostyrylacridine methochloride showed slight trypanocidal activity, but 5-*m*-aminostyrylacridine methochloride showed none. 5-*p*-Dimethylaminostyrylacridine methochloride also had no trypanocidal properties, but was much more toxic—the tolerated dose for a 20-g. mouse being 0·1 mg. as compared with 2—3 mg. of the other two.

(c) *On amino*-5-*aminostyrylacridines*. In every case the quaternary compound was a much more potent antiseptic than the corresponding non-quaternary base. Also, whereas the latter lacked trypanocidal action, the methochlorides had some effect, although 3-amino-5-*p*-aminostyrylacridine methochloride and 3-amino-5-*p*-aminostyryl-7-methylacridine methochloride were somewhat more toxic. The introduction of amino-groups at position 3 or positions 3 and 7 into 5-*p*-aminostyrylacridine methochloride hydrochloride had no great effect on antiseptic or trypanocidal action or toxicity.

The work will be continued. It is proposed to attempt to prepare 2-amino- and 2 : 8-diamino-derivatives of methyl- and styryl-acridines and to investigate their therapeutic properties.

Experimental.

o-Chloroacetophenone was prepared by a modification of Thorp and Brunskill's method (*J. Amer. Chem. Soc.*, 1915, **37**, 1258). The mixture of sodium ethoxide, *o*-chlorobenzoyl chloride, and ethyl acetoacetate was kept at 0—5° for 3—4 days instead of 24 hours and the sodio-derivative of ethyl *o*-chlorobenzoylacetoacetate, thus obtained in increased yield, was heated with ammonia and ammonium chloride for 6 hours instead of 2—3 hours. Since the ester itself separated as a heavy oil, extraction with ether was omitted and the ester was washed with a little dilute sulphuric acid and used as such without drying. The overall yield of the ketone from *o*-chlorobenzoyl chloride was 54%; it boiled at 228—229°/758 mm. (lit., 227—228°/738 mm.). It was converted, as described by Thorp and Brunskill, into 2-chloro-5-nitroacetophenone, which was converted into 3-nitro-5-methylacridine by the two-stage method of Jensen and Rethwisch (*loc. cit.*) with modifications. 7 G. of 2-chloro-5-nitroacetophenone were dissolved in 7 c.c. of freshly distilled aniline in the warm, 7 g. of anhydrous potassium carbonate added, and the whole heated with stirring at 125° (± 5°) for 6 hours. While still warm, the mass was stirred with 20 c.c. of alcohol and kept overnight. The yellow solid was collected, washed with a little cold alcohol, then water, allowed to dry in air, and recrystallised from alcohol (carbon); yield, 73% of 4-nitro-2-acetyldiphenylamine, m. p. 130° (lit., 125°) (Found: C, 65·7; H, 4·7; N, 10·9. Calc.: C, 65·6; H, 4·7; N, 10·9%). Ring closure was effected with concentrated sulphuric acid (5 g. of substance, 50 c.c. of glacial acetic acid, 2·5 c.c. of sulphuric acid, 2 hours at 130°), the mixture poured into water, and the acridine precipitated with ammonia; yield 79%. The resulting 3-nitro-5-methylacridine (Found: C, 70·5; H, 4·2; N, 11·5. Calc.: C, 70·6; H, 4·2; N, 11·7%) was best recrystallised from benzene. A chloroform solution showed a brilliant yellowish-green fluorescence in ultra-violet light, but not in daylight, instantly destroyed by a drop of aniline.

3-Amino-5-methylacridine.—This was prepared as for 3-amino-5-phenylacridine (Ullmann and Ernst, *loc. cit.*), 1 g. of 3-nitro-5-methylacridine being used. The hydrochloride of the base did not, however, separate from the solution after removal of tin hydroxide. A slight excess of ammonia was therefore added, and the yellow precipitate of the free base extracted with ether. After washing with water and evaporation, the substance remained as a reddish-brown solid which could not be crystallised satisfactorily. The best procedure, which, however, did not give a pure product, was to dissolve the substance in warm alcohol, add an equal volume of warm water, boil for a few minutes (carbon), and allow the alcohol to evaporate slowly from the filtrate on the water-bath. At a certain concentration the base separated in reddish-brown crystalline tufts, which were washed with aqueous alcohol and allowed to dry; yield, 84%. It was contaminated with resinous matter and had m. p. about 200° (decomp.). The amine was soluble in the common solvents, except water, and sparingly soluble in benzene and light petroleum. The *acetyl* derivative, prepared with acetic anhydride and anhydrous sodium acetate, separated from aqueous alcohol (carbon) as a pale yellow, crystalline powder (yield, 87%), decomposing at about 260° but remaining unmelted at 360° (Found: C, 76·8; H, 5·5; N, 11·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). It was soluble in alcohol and in glacial acetic acid, sparingly soluble or insoluble in other common solvents, and soluble in dilute hydrochloric acid.

3-Acetamido-5-methylacridine metho-p-toluenesulphonate, prepared from this acetyl derivative (1 g.) by heating with methyl *p*-toluenesulphonate (1 mol.) at 145° for 2 hours with occasional stirring and crystallised first from alcohol and then by precipitation of an alcoholic solution with dry ether, formed yellow-brown crystals (0·7 g.), m. p. 226° (Found: N, 6·5; S, 7·4. $C_{24}H_{24}O_4N_2S$ requires N, 6·4; S, 7·3%), easily soluble in alcohol and in water with intense greenish fluorescence. The acridinium base was precipitated as a blue-green solid on addition of ammonia to the aqueous solution. 2 G. of this salt in 3·5 c.c. of water were refluxed for 1 hour with an equal volume of concentrated hydrochloric acid, the solution evaporated to dryness on the water-bath, the residue dissolved in water, and the filtered, deep red solution exactly neutralised with dilute potassium carbonate solution. 3 G. of potassium iodide were added with shaking, a purplish-red precipitate (1 g.) of 3-amino-5-methylacridine methiodide being formed, easily soluble in alcohol, sparingly soluble in water. This precipitate was boiled with excess of freshly precipitated silver chloride in aqueous methyl alcohol for 8 hours; the deep red filtrate and washings on evaporation on the water-bath left 0·7 g. of the dark violet-red, crystalline *3-amino-5-methylacridine methochloride*, which could be recrystallised from alcohol–ether (Found: N, 10·6; Cl, 13·6. $C_{15}H_{15}N_2Cl$ requires N, 10·8; Cl, 13·7%). It was slightly hygroscopic, gave a deep red solution in water, and melted above 200° (decomp.).

3-Nitro-7-amino-5-methylacridine.—2-Chloro-5-nitroacetophenone, *p*-aminoacetanilide, and anhydrous potassium carbonate (5 g. of each) were heated at 125° for 3 hours. The powdered brown product, after washing with water, then alcohol, gave on recrystallisation from alcohol (carbon) golden-yellow plates of *4-nitro-4′-acetamido-2-acetyldiphenylamine*, m. p. 207° after reddening at about 120° (Found: C, 61·3; H, 4·9; N, 13·2. $C_{16}H_{15}O_4N_3$ requires C, 61·3; H, 4·8; N, 13·4%); yield, 72%. It was soluble in warm alcohol, chloroform, acetone, and glacial acetic acid, but sparingly soluble in other common solvents. To effect ring closure, 5 g. of the substance in 50 c.c. of glacial acetic acid and 2·5 c.c. of concentrated sulphuric acid were heated under reflux at 125° for 2½ hours; the mixture was poured into water containing a slight excess of ammonia, and the washed and dried dark red precipitate recrystallised twice from benzene. The resulting *3-nitro-7-amino-5-methylacridine* was a brick-red crystalline powder, decomposing at about 270°, but still unmelted at 380° (Found: C, 66·0; H, 4·2; N, 16·4. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·3; N, 16·6%); yield, 94%. It was soluble in acetone and in acids, but insoluble or sparingly soluble in other solvents. The *acetyl* derivative separated from aqueous alcohol (carbon) as a yellow crystalline powder, darkening at about 280°, but unmelted at 360° (Found: C, 65·7; H, 4·5; N, 14·2. $C_{16}H_{13}O_3N_3$ requires C, 65·1; H, 4·4; N, 14·2%); it was moderately soluble in warm alcohol and was easily deacetylated by boiling with concentrated hydrochloric acid.

3 : 7-Diamino-5-methylacridine.—The preceding nitro-amine (2 g.) was reduced in the cold by means of the anhydrous stannous chloride reagent (Albert and Linnell, J., 1936, 1614). To the deep red aqueous solution of the greenish-brown stannichloride, excess of sodium hydroxide solution was added and the brown precipitate of the diamine was collected, washed with water, and allowed to dry; yield, 1·2 g. It did not crystallise satisfactorily from solvents, and sintered at about 200° (decomp.). It was converted in good yield into the *diacetyl* derivative, a substance still unmelted at 360° and crystallising from aqueous alcohol (carbon) as a yellow-brown powder (Found: C, 71·0; H, 5·4; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·4; H, 5·5; N, 13·7%). In general properties it resembled 3-acetamido-5-methylacridine. This diacetyl derivative was converted through the metho-*p*-toluenesulphonate, exactly by the same procedure as before with similar yield, into *3 : 7-diamino-5-methylacridine methochloride*, which separated from alcohol–ether as a reddish-brown, crystalline, hygroscopic powder, decomp. about 200°, easily soluble in water with a deep reddish-brown colour (Found: N, 15·4; Cl, 13·1. $C_{15}H_{16}N_3Cl$ requires N, 15·3; Cl, 13·0%).

4-Nitro-3′-acetamido-2-acetyldiphenylamine was prepared in 62% yield in exactly the same way as the 4′-acetamido-compound described above, *m*-aminoacetanilide being used, and possessed similar properties; it formed yellow crystals, m. p. 229° (Found: C, 61·6; H, 5·0; N, 13·2. $C_{16}H_{15}O_4N_3$ requires C, 61·3; H, 4·8; N, 13·4%).

4-*Nitro*-2-*acetyl*-4'-*methyldiphenylamine*.—This was prepared in the same way as 4-nitro-2-acetyldiphenylamine, which it closely resembled, *p*-toluidine being used instead of aniline and heating continued only for 3 hours; yield, 77% (Found: C, 66·8; H, 5·4; N, 10·2. $C_{15}H_{14}O_2N_2$ requires C, 66·6; H, 5·2; N, 10·4%). It formed yellow crystals, m. p. 132°. From this compound, 3-*nitro*-5 : 7-*dimethylacridine* was prepared by ring closure as before (heating at 125° for 2½ hours; crystallisation from benzene). The yellow crystals decomposed at about 235° but remained unmelted at 360°; yield, 90% (Found: C, 72·0; H, 4·9; N, 11·0. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). The substance dissolved in dilute hydrochloric acid, was easily soluble in chloroform, in which it fluoresced bright yellow-green in ultra-violet light but only feebly in daylight, and soluble in hot alcohol, benzene, acetone, and glacial acetic acid. From it, 3-amino-5 : 7-dimethylacridine was prepared by reduction with the anhydrous stannous chloride reagent as before; the amine precipitated from the solution of the stannichloride by excess of sodium hydroxide was extracted with ether. Evaporation of the ether left a brown solid, which was purified to a certain extent by recrystallisation from aqueous alcohol (carbon) but could not be obtained pure; yield, 80%. The substance decomposed at about 170° and in general properties resembled 3-amino-5-methylacridine. Acetylation gave 3-*acetamido*-5 : 7-*dimethylacridine* (yield, 84%), which separated from aqueous alcohol (carbon) as a pale yellow, crystalline powder, decomposing at about 250° but still unmelted at 360°; in general properties it resembled 3-acetamido-5-methylacridine (Found: C, 77·0; H, 6·3; N, 10·7. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1; N, 10·6%). From it was obtained, in the usual manner, 3-*amino*-5 : 7-*dimethylacridine methochloride*, which formed, from absolute alcohol and ether, reddish-brown crystals decomposing above 200°. It was slightly hygroscopic and gave a deep red solution in water (Found: N, 10·4; Cl, 12·9. $C_{16}H_{17}N_2Cl$ requires N, 10·3; Cl, 13·0%).

α-(o-*Nitrophenyl*)-β-5-(3-*nitroacridyl*)*ethanol*, obtained by heating 1·19 g. of 3-nitro-5-methylacridine and 0·76 g. of *o*-nitrobenzaldehyde at 100° for 6 hours, washing the powdered product with alcohol, pyridine, then alcohol, and recrystallising it from benzene, formed small yellow crystals (1 g.), decomposing at 170° but still unmelted at 360°. It was only sparingly soluble in dilute or concentrated hydrochloric acid and the common organic solvents (Found: C, 65·0; H, 3·8; N, 10·9. $C_{21}H_{15}O_5N_3$ requires C, 64·8; H, 3·9; N, 10·8%).

α-(m-*Nitrophenyl*-β-5-(3-*nitroacridyl*)*ethanol*, prepared in the same way, separated from alcohol–pyridine in yellow crystals (1 g.), decomp. 175°, and closely resembled the preceding compound (Found: C, 65·0; H, 3·9; N, 10·8%).

3-*Nitro*-5-p-*nitrostyrylacridine*.—3-Nitro-5-methylacridine (2·38 g.) and *p*-nitrobenzaldehyde (1·5 g.), which, when heated alone or with zinc chloride, did not seem to react or else gave tar, were refluxed in 6 c.c. of acetic anhydride at 130° for 3 hours. The cold solid product was collected, washed with a little warm alcohol, and recrystallised from pyridine. It formed yellow crystals (1·7 g.) darkening above 250° but still unmelted at 360° and was sparingly soluble in the common solvents (Found: C, 68·2; H, 3·6; N, 11·2. $C_{21}H_{13}O_4N_3$ requires C, 67·9; H, 3·5; N, 11·3%). 3-Amino-5-*p*-aminostyrylacridine, prepared from the above compound (1·5 g.) by reduction with the anhydrous stannous chloride reagent as before, separated from the violet-red aqueous solution of the stannichloride, on addition of excess of sodium hydroxide solution, as a brown precipitate (1·2 g. after washing and drying). It could not be crystallised satisfactorily from solvents, decomposed above 200°, and in solubility resembled 3-amino-5-methylacridine. It (1 g.) was converted into the *diacetyl* derivative, which separated from aqueous alcohol (carbon) as a yellow-brown crystalline powder (1 g.), unmelted at 360° (Found: C, 76·5; H, 5·2; N, 10·5. $C_{25}H_{21}O_2N_3$ requires C, 76·0; H, 5·3; N, 10·6%). In general solubility it resembled 3-acetamido-5-methylacridine. It was converted as usual into 3-*amino*-5-p-*aminostyrylacridine methochloride*, the intermediate metho-*p*-toluenesulphonate being obtained by using 2½ mols. of methyl *p*-toluenesulphonate. This methochloride separated from alcohol–ether as a dark purplish, crystalline powder decomposing at about 250° and easily soluble in water to a violet-red solution; yield, 0·3 g. from 1 g. of the above diacetyl derivative (Found: N, 11·4; Cl, 9·8. $C_{23}H_{20}N_3Cl$ requires N, 11·6; Cl, 9·8%).

3-*Nitro*-5-p-*nitrostyryl*-7-*methylacridine* was prepared as above and in similar yield, from 3-nitro-5 : 7-dimethylacridine and *p*-nitrobenzaldehyde. Although 2 mols. of *p*-nitrobenzaldehyde were used, only one reacted, evidently, as expected, with the 5-methyl group only. The substance crystallised from pyridine as a brownish-yellow powder, unmelted at 360° and sparingly soluble in the common solvents (Found: C, 68·3; H, 3·8; N, 10·9. $C_{22}H_{15}O_4N_3$ requires C, 68·6; H, 3·9; N, 10·9%). Reduction of 2 g. of this substance by the anhydrous stannous chloride reagent gave 1·5 g. of 3-amino-5-*p*-aminosytryl-7-methylacridine. Like 3-amino-5-methylacridine, which it resembled in solubility, it could not be crystallised satisfactorily, forming a yellow-brown powder, decomp. about 200°. It was converted into the *diacetyl* derivative, which separated from aqueous alcohol (carbon) as a yellow-brown powder, unmelted at 360°, resembling 3-acetamido-5-methylacridine in yield and solubility (Found: C, 76·5; H, 5·5; N, 10·2. $C_{26}H_{23}O_2N_3$ requires C, 76·2; H, 5·6; N, 10·3%). It (1 g.) was converted in the usual way into 3-*amino*-5-p-*aminostyryl*-7-*methylacridine methochloride* (0·35 g.); this closely resembled the preceding methochloride in properties, decomposed above 250°, was slightly hygroscopic, and was easily soluble in water to a dark red solution (Found: N, 11·0; Cl, 9·5. $C_{23}H_{22}N_3Cl$ requires N, 11·2; Cl, 9·4%).

3-*Nitro*-7-*acetamido*-5-p-*nitrostyrylacridine* was prepared by heating 1·48 g. of 3-nitro-7-acetamido-5-methylacridine with 0·76 g. of *p*-nitrobenzaldehyde in 4 c.c. of acetic anhydride according to previous procedure. It separated from pyridine as a yellow-brown powder (0·95 g.), darkening above 250° but still unmelted at 360° (Found: C, 64·0; H, 3·6; N, 13·1. $C_{23}H_{16}O_5N_4$ requires C, 64·5; H, 3·7; N, 13·1%), and sparingly soluble in the common solvents. This substance (1 g.) was reduced and the base liberated, in the manner already described, was heated for 1 hour with 15% hydrochloric acid at 100° to complete deacetylation. From this solution 3 : 7-diamino-5-*p*-aminostyrylacridine was precipitated as a brown, somewhat resinous solid (0·7 g.), decomposing at about 180°, and in general solubility resembling 3-amino-5-*p*-aminostyrylacridine. It could not be crystallised satisfactorily and was (1 g.) in the usual manner converted by acetylation into 3 : 7-*bis*(*acetamido*)-5-p-*acetamidostyrylacridine* (0·9 g.), a yellow-brown crystalline powder from aqueous alcohol (carbon), unmelted at 360° and resembling 3-acetamido-5-methylacridine in general solubility (Found: C, 71·4; H, 5·4; N, 12·3. $C_{27}H_{24}O_3N_4$ requires C, 71·6; H, 5·3; N, 12·4%). It was converted into 3 : 7-*diamino*-5-p-*aminostyrylacridine methochloride*, the intermediate metho-*p*-toluenesulphonate being obtained by using 2½ mols. of the ester; the methiodide was a dark purplish solid slightly soluble in water, easily soluble in alcohol. The methochloride separated from alcohol–ether as a dark brown powder, decomposing at about 200° and readily soluble in water to a deep reddish-brown solution (Found: N, 15·0; Cl, 9·3. $C_{23}H_{21}N_4Cl$ requires N, 14·9; Cl, 9·4%); yield, 0·3 g. from 1 g. of the triacetyl derivative above.

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91. *Further Observations on the Optically Active αγ-Dimethylallyl Alcohols.*

By Michael P. Balfe, Henry W. J. Hills, Joseph Kenyon, Henry Phillips, and Bertie C. Platt.

Hills, Kenyon, and Phillips (J., 1936, 576), described the erratic mutarotation of (+)-αγ-dimethylallyl alcohol and the preparation of an unusual *lævo*-alcohol,* from the lævo-chloride. These peculiarities are not shown by other substituted allyl alcohols. On the other hand, the general conclusion that these alcohols and their derivatives can undergo anionotropic rearrangement, which is accompanied by partial racemisation, does not explain the peculiarities of αγ-dimethylallyl alcohol.

Re-examination of the (+)alcohol indicates that during the mutarotation a lævorotatory substance is formed which is also present in the alcohol obtained from the *lævo*-chloride. The nature of this substance has not been elucidated, but it would appear to form only a small proportion of the alcohols in which it occurs.

(+)-αγ-Dimethylallyl alcohol yields, with a variety of reagents, *lævo*-αγ-dimethylallyl chloride (2-chloro-Δ^{γ}-pentene; Hills, Kenyon, and Phillips, *loc. cit.*; Levene and Haller, *J. Biol. Chem.*, 1929, **81**, 703), with $\alpha_{5461}^{20°}$ ranging from − 1° to − 19° (*l*, 1). The chloride racemises on standing, as it does in benzene or acetone solution in presence of stannic or mercuric chloride (Böhme, *Ber.*, 1938, **71**, 2372), presumably on account of the lability of the chlorine atom.

Solvolytic reactions (see following table) of the chloride with methyl and *n*-butyl alcohol give extensively racemised products. This is to be expected, since these reactions are initiated by ionisation of the chloride (compare the reactions of α- and γ-methylallyl chlorides with ethyl alcohol; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627). Replacement reactions of the chloride with solid potassium or silver acetate also result in much racemisation, possibly due to the heterogeneous reaction conditions (see Cowdrey, Hughes, Ingold, Masterman, and Scott, J., 1937, 1252).

The homogeneous reaction with sodium methoxide also gives a highly racemised product. Bergmann (*Helv. Chim. Acta*, 1937, **20**, 590) observed complete racemisation in the reaction of *lævo*-αγ-dimethylallyl chloride with the sodium derivatives of benzhydrol (in ethyl ether) and of ethyl malonate (in ethyl alcohol). These racemisations suggest that even the homogeneous replacement reactions are controlled by the unimolecular (ionisation) mechanism; this conclusion is not improbable, in view of the ease with which αγ-disubstituted allyl derivatives react by this mechanism (Balfe, Hills, Kenyon, Phillips, and Platt, J., 1942, 556). On the other hand, the bimolecular mechanism predominates in the reactions of monoalkyl-substituted allyl chlorides with sodium ethoxide, since Hughes (*loc. cit.*) found that no rearrangement occurred during the interaction of α- and γ-methylallyl chlorides with sodium ethoxide in ethyl alcohol (confirmed by Roberts, Young, and Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2157).

Reactions of αγ-dimethylallyl chloride.

$\alpha_{5461}^{20°}$ (*l*, 1).*	Reactant.	Product.	Optical purity of product, %.	$\alpha_{5461}^{20°}$ (*l*, 1).*	Reactant.	Product.	Optical purity of product, %.
−7·1°	MeOH	Methyl ether	1·3	−11·2°	AgOAc	Acetate	2·1
−2·9	*n*-BuOH	*n*-Butyl ether	1·6	+ 6·8	NaOMe	Methyl ether	3·5
−1·1	KOAc	Acetate	0·3				

* Maximum recorded, 19°.

The hydrolysis of αγ-dimethylallyl chloride by water is kinetically unimolecular (Arcus and Smith, J., 1939, 1748) and would therefore be expected to be accompanied by much racemisation, as are the hydrolyses of γ-methyl-α-propylallyl chloride (Arcus and Kenyon, J., 1938, 1912) and of γ-methyl-α-ethylallyl chloride (Airs, Balfe, and Kenyon, J., 1942, 18). The *lævo*-chloride prepared from the (+) alcohol yields on hydrolysis a *lævo*-alcohol similar in magnitude of rotatory power to the (+)alcohol. This result is unexpected, because optically active halides on hydrolysis usually yield alcohols of the same sign of rotation as that of the parent alcohol.

By methods which produce optically active derivatives from (+)- or (−)-αγ-dimethylallyl alcohol, this *laevo*-alcohol yields a hydrogen phthalate and a methyldibromo-*n*-propylcarbinol, both optically inactive. It, therefore, does not contain the normal form of (−)-αγ-dimethylallyl alcohol. Certain optically active derivatives can, however, be prepared from the *lævo*-alcohol; the acetate has $\alpha_{5461}^{18°}$ − 0·66° (*l*, 1) and the reduction product (methyl-*n*-propylcarbinol) has $\alpha_{5461}^{18°}$ + 0·3° (*l*, 1); these values are about 2% of those of the corresponding derivatives from (+)-αγ-dimethylallyl alcohol.

These observations are best explained by assuming that the major product of the hydrolysis of the *lævo*-chloride is *dl*-dimethylallyl alcohol, but that it contains some source of optical activity. The occurrence or absence of optical activity in derivatives prepared from this alcohol could then be accounted for by different rates of reaction of the *dl*-alcohol and the optically active substance, or removal of this substance during purification of the derivatives. Our investigations have not revealed the nature of the optically active substance.

During the preparation and hydrolysis of γ-methyl-α-ethyl- and -α-*n*-propyl-allyl chlorides (Airs, Balfe,

* We use (+) and (−) to refer to the sign of rotatory power of optically pure substances, and *dextro-* and *lævo-* for substances of unspecified optical purity. We define as (+), the αγ-dimethylallyl alcohol which, when freshly prepared from the (+)hydrogen phthalate by hydrolysis with 5N-sodium hydroxide, is dextrorotatory (homogeneous) in the visible spectrum at 20°. The alcohol which Levene and Haller (*loc. cit.*) described as *l*-, because it gave a lævorotatory solution in ethyl ether, is the (+)alcohol, as is shown by the results of Hills, Kenyon, and Phillips (*loc. cit.*).

and Kenyon; Arcus and Kenyon, *locc. cit.*), rearrangement and racemisation occur, without the optical peculiarities observed with αγ-dimethylallyl chloride.

As the following evidence suggests, it appears that a lævorotatory substance is also formed during the mutarotation of (+)-αγ-dimethylallyl alcohol: (i) the mutarotation, though erratic, leads to a fall in rotatory power, with eventual change in sign ((Hills, Kenyon, and Phillips, *loc. cit.*); (ii) a specimen of the alcohol, having $\alpha^{20°}_{5461}$ + 0·70°, $\alpha^{70°}_{5461}$ − 2·66°, after 48 hours at 70° had $\alpha^{70°}_{5461}$ −3·22° and, after cooling, $\alpha^{20°}_{5461}$ + 0·47° (*l*, 1); (iii) the alcohol recovered from the interaction of (+)-αγ-dimethylallyl alcohol (1 mol.) and phenyl carbimide (0·5 mol.) is lævorotatory, but from (+)alcohol which has become lævorotatory during mutarotation the recovered alcohol is also lævorotatory. The last experiment suggests that the *lævo*-substance is present even in the alcohol which we define as (+). This was usually purified by redistillation to b. p. 120—122° and prepared from phthalate which had been several times recrystallised in the form of its brucine salt, and in some cases had also been recrystallised after removal of the brucine. Distillation of the alcohol freshly prepared from the phthalate yields a small fraction of lower b. p. (119—121°) and lower dextrorotation ($\alpha^{20°}_{5461}$ + 0·18°, $\alpha^{20°}_{4358}$ + 1·58°) than the main fraction (b. p. 121—122°; $\alpha^{20°}_{5461}$ + 0·60°, $\alpha^{20°}_{4358}$ + 2·25°, *l*, 1), so the lævorotatory substance may have a lower b. p. than αγ-dimethylallyl alcohol (both fractions undergo the characteristic mutarotation). The presence of a lævorotatory substance would be a cause of the anomalous rotatory dispersion (Hills, Kenyon, and Phillips, *loc. cit.*; Levene, and Rothen, *J. Chem. Physics*, 1937, **5**, 980), though this is equally well explained by the unsaturation of the alcohol. On standing, peroxides and acids are formed in the alcohol, but our evidence indicates that the formation of these is not the cause of the mutarotation. Although the boiling range of the crude alcohol suggests the presence of some αγ-dimethylallyl ether (b. p. 156—157°), the above observations were made with alcohol which had been redistilled to a b. p. within 120—122°.

The hydrogen phthalate prepared from the alcohol at various stages of its mutarotation diminishes (by not more than 10%) in rotatory power, but this change is much less marked than that of the parent alcohol, and the sign of rotation of the phthalate is always the same, even when that of the alcohol from which it is prepared has reversed. The very low rotatory power of the alcohol would, of course, be sensitive to the presence of traces of other optically active substances.

Since αγ-dimethylallyl alcohol is the only α-methyl-substituted allyl alcohol which we have examined, we have considered whether its peculiarities may be due to the formation of methylallylcarbinol, through electron release from the α-methyl group (Baker and Nathan, J., 1935, 1844; Hughes, Ingold, and Taher, J., 1940, 949). The properties of the carbinol would agree with this suggestion: it has b. p. 115—116° (Stöhr, *Ber.*, 1939, **72**, 1138), $\alpha^{20°}_{5893}$ − 4·4 (*l*, 1), and its hydrogen phthalate has $[\alpha]_{5893}$ − 7·8° in ethyl ether; the last two values are calculated from those given for the *lævo*-carbinol by Levene and Haller (*loc. cit.*), using the ratio between the rotatory power of its reduction product and that of optically pure methyl-*n*-propylcarbinol (Pickard and Kenyon, J., 1911, **99**, 49). However, we have not been able to isolate the α-naphthylurethane of methylallylcarbinol from that of the alcohol obtained from αγ-dimethylallyl chloride or of αγ-dimethylallyl alcohol which has been kept for a long time.

The mutarotation of other substituted allyl alcohols may often involve some racemisation occurring as a concomitant of anionotropic rearrangement. This has been shown to be the cause of the partial racemisation of γ-methyl-α-ethylallyl alcohol (Airs, Balfe, and Kenyon, *loc. cit.*) and may therefore be taken to apply to that of αγ-diethylallyl alcohol (Platt, J., 1941, 316). Owing to the same cause, γ-phenyl-α-methylallyl alcohol loses some 10% of its rotatory power during 2 years, as does α-phenyl-γ-methylallyl alcohol (Kenyon, Partridge and Phillips, J., 1937, 207). Similarly, the rotation of a specimen of *lævo*-α-phenylallyl alcohol (Duveen and Kenyon, J., 1939, 1697) changed from $\alpha^{20°}_{5461}$ − 23·1° to $\alpha^{20°}_{5461}$ − 18·8° (*l*, 2) in 4 years; hydrogen phthalates prepared from the alcohol before and after mutarotation had $[\alpha]_{5893}$ + 37·8° and 27·0° (in carbon disulphide). Only in one other case have we observed reversal of sign during mutarotation. A specimen of *lævo*-γ-methyl-α-*n*-propylallyl alcohol (Arcus and Kenyon, J., 1938, 312), during 4 years at room temperature, changed from $\alpha^{17°}_{5461}$ − 5·44° to $\alpha^{20°}_{5461}$ + 5·40 (*l*, 2); hydrogen phthalates from the alcohol before and after mutarotation had $[\alpha]_{5461}$ − 6·8° and − 2·9°, respectively, in ethyl alcohol. This change, which merits further investigation, may be due to rearrangement to α-methyl-γ-*n*-propylallyl alcohol (the rotatory power of which is unknown), accompanied by some racemisation.

The above six examples are in harmony with the suggestion that mutarotation of the unsymmetrically substituted allyl alcohols is due to anionotropic rearrangement with concomitant racemisation. This does not explain the mutarotation of αγ-dimethylallyl alcohol. On account of its symmetrical substitution, change in sign of rotation during rearrangement of the (+)alcohol would be due to formation of *lævo*-dimethylallyl alcohol, and a rearranged alcohol should give a *lævo*-phthalate, which is contrary to our observations.

Experimental.

dl-, (+)-, and (−)-αγ-Dimethylallyl alcohols were prepared as described by Hills, Kenyon, and Phillips (*loc. cit.*).

Preparation of αγ-Dimethylallyl Chloride.—(i) *By means of thionyl chloride.* (+)-αγ-Dimethylallyl alcohol (16 g.) was added slowly to thionyl chloride (22 g.) at 0°. After warming to room temperature, the product was dissolved in ether, washed with water, and the ether removed after drying. The residual αγ-dimethylallyl chloride had b. p. 101°, $n^{12°}_{5893}$ 1·4352 (Found: C, 56·9; H, 8·6; Cl, 33·3. Calc. for C_5H_9Cl: C, 57·4; H, 8·6; Cl, 34·0%). From (−)alcohol with $\alpha^{14°}_{5893}$ − 0·99°, $\alpha^{14°}_{5461}$ − 1·40°, $\alpha^{14°}_{4358}$ − 3·78° (*l*, 2), the chloride had α_{5893} + 0·21°, α_{5461} + 0·29° (*l*, 2), and gave on hydrolysis an alcohol with $\alpha^{20°}_{5893}$ + 0·12°, $\alpha^{20°}_{5461}$ + 0·19° (*l*, 0·25). A similar experiment, in which the (−)alcohol (25 g.)

was first dissolved in a mixture of dry ether (100 c.c.) and pyridine (26·5 g.), gave 14 g. of chloride, b. p. 22°/14 mm., $\alpha^{20°}_{5893}$ + 31·3°, $\alpha^{20°}_{5461}$ + 38·4°, $\alpha^{20°}_{4358}$ + 74·0° (*l*, 2).

(ii) *By means of phosphorus trichloride and pyridine.* This is the better method. A mixture of the alcohol (32·6 g.) and pyridine (6·8 g.) was run slowly into redistilled phosphorus trichloride (20 g.) at 0°. After warming to room temperature, the upper layer was separated and distilled, yielding 23 g. of chloride, b. p. 20°/12 mm. From *dextro*-alcohol, $\alpha^{16°}_{5893}$ + 1·12°, $\alpha^{16°}_{5461}$ + 1·63°, $\alpha^{16°}_{4358}$ + 4·94° (*l*, 2), the chloride had $\alpha^{17°}_{5893}$ − 8·92°, $\alpha^{17°}_{5461}$ − 10·74° (*l*, 2). From *dextro*-alcohol, $\alpha^{21°}_{5893}$ + 0·52°, $\alpha^{21°}_{5780}$ 0·84°, $\alpha^{21°}_{5461}$ + 1·18°, $\alpha^{21°}_{4358}$ + 4·30° (*l*, 2), the chloride had $\alpha^{18°}_{5893}$ − 4·61°, $\alpha^{18°}_{5780}$ − 4·87°, $\alpha^{18°}_{5461}$ − 5·59°, $\alpha^{18°}_{4358}$ − 10·65 (*l*, 0·5). From *lævo*-alcohol, $\alpha^{19°}_{5461}$ − 0·70° (*l*, 2), a chloride was obtained with $\alpha^{18°}_{5893}$ + 12·09°, $\alpha^{18°}_{5461}$ + 14·75°, $\alpha^{18°}_{4358}$ + 28·1° (*l*, 2). In the absence of pyridine, reaction with phosphorus trichloride yields a racemic chloride. The chloride is a pungent liquid which evolves hydrogen chloride, particularly on heating, and the decrease in its rotatory power with increasing temperature is probably due to decomposition.

Reactions of αγ-Dimethylallyl Chloride.—(i) *With methyl alcohol.* The chloride (4·5 g.), $\alpha^{16°}_{5461}$ − 15·14° (*l*, 2), prepared from (+)alcohol, was shaken intermittently during 24 hours with dry methyl alcohol (20 c.c.) and calcium carbonate (2·3 g.). The mixture was then gently warmed, treated with anhydrous calcium chloride to remove excess of methyl alcohol, and then extracted with ether. From the dried ethereal extract, methyl αγ-dimethylallyl ether (2·5 g.) was obtained; b. p. 89—89·5°, $n^{14·5°}_{5893}$ 1·4031, $\alpha^{18°}_{5893}$ − 0·33°, $\alpha^{18°}_{5780}$ −0·36°, $\alpha^{18°}_{5461}$ − 0·38°, $\alpha^{18°}_{4358}$ − 0·50° (*l*, 0·5).

(ii) *With n-butyl alcohol.* The chloride (4 g.), α_{5461} + 1·47° (*l*, 0·5), was warmed for 3 hours on the steam-bath with *n*-butyl alcohol (15 c.c.) and calcium carbonate (2 g.). The cooled product was diluted with ether and filtered; from the dried filtrate *n*-butyl αγ-dimethylallyl ether was obtained, b. p. 150—151°, $n^{18°}_{5893}$ 1·4100, $\alpha^{17°}_{5461}$ + 0·24° (*l*, 0·5).

(iii) *With potassium acetate.* The chloride (5 g.), $\alpha^{20°}_{5461}$ − 0·54° (*l*, 0·5), was warmed on the steam-bath with potassium acetate (8 g.) which had been moistened with water. Calcium carbonate was added and the mixture extracted with ether. The dried, filtered extract was distilled. Redistillation of the fraction, b. p. 120—140°, gave αγ-dimethylallyl acetate (2 g.), b. p. 135—136°, $n^{15°}_{5893}$ 1·4200, $\alpha^{15°}_{5461}$ + 0·10°, $\alpha^{15°}_{5893}$ + 0·08° (*l*, 0·5). The chloride did not react with dry potassium acetate, in the absence of solvent or with acetone or benzene as diluents.

(iv) *With silver acetate.* The chloride (4 g.), $\alpha^{18°}_{5893}$ − 4·61°, $\alpha^{18°}_{5461}$ − 5·59°, $\alpha^{18°}_{4358}$ − 10·65° (*l*, 0·5), was triturated with 17 g. of silver acetate at 0°; a vigorous reaction occurred. The mixture was diluted with ether, filtered, dried (calcium chloride), and distilled. The αγ-dimethylallyl acetate produced had, after redistillation, b. p. 37—40°/15 mm., $n^{19°}_{5893}$ 1·4112, $\alpha^{18°}_{5893}$ − 0·28°, $\alpha^{18°}_{5780}$ − 0·30°, $\alpha^{18°}_{5461}$ − 0·35°, $\alpha^{18°}_{4358}$ − 0·66° (*l*, 0·25).

(v) *With sodium methoxide. lævo-*αγ-Dimethylallyl alcohol (16·3 g.), $\alpha^{20°}_{5461}$ − 0·51° (*l*, 1), prepared from phthalate of $[\alpha]_{5461}$ − 20·4° in chloroform, was converted (pyridine–phosphorus trichloride) into the chloride (11 g.; $\alpha^{22°}_{5461}$ + 6·76°, *l*, 1); this (5 g.) was warmed for 5 mins. with sodium methoxide (2·5 mols.) in methyl alcohol (50 c.c.), the solution diluted with water, and extracted with ether. From the dried ethereal extract, methyl αγ-dimethylallyl ether (2 g.) was obtained, b. p. 90—91°/760 mm., $n^{21°}_{5893}$ 1·4243, $\alpha^{21°}_{5461}$ + 0·50° (*l*, 0·25).

Hydrolysis of αγ-Dimethylallyl Chloride.—This was conducted with an aqueous suspension of calcium carbonate (Hills, Kenyon, and Phillips, *loc. cit.*). (i) Chloride of $\alpha^{18°}_{4358}$ + 28·1° (*l*, 2) (see above) gave alcohol of b. p. 120°, $n^{19°}_{5893}$ 1·4288, $\alpha^{17°}_{5893}$ + 1·50°, $\alpha^{17°}_{5461}$ + 1·66°, $\alpha^{17°}_{4358}$ + 2·90° (*l*, 2) (Found: C, 69·4; H, 11·6. Calc. for $C_8H_{10}O$: C, 69·8; H, 11·6%). Other results are summarised below:

αγ-Dimethylallyl alcohol.		αγ-Dimethylallyl chloride.		Alcohol obtained from the chloride.	
$\alpha^{t°}_{5461}$; *l*, 1.	*t*.	$\alpha^{t°}_{5461}$; *l*, 1.	*t*.	$\alpha^{t°}_{5461}$; *l*, 1.	*t*.
−0·15°	22°	+0·64°	22°	+0·14°	22°
−0·13	20	+0·44	20	+0·18	21
−0·21	22	+6·40	20	+0·54	18
−0·13	20	+3·91	12	+0·73	15
−0·35	20	+4·66	19	+0·74	17
−0·35	20	+7·37	18	+0·90	18

(ii) A specimen of the (+)alcohol (originally $\alpha^{22°}_{5461}$ + 0·10°; *l*, 0·25), which after mutarotation for 20 months had $\alpha^{5°}_{5461}$ − 1·05° (*l*, 1), gave a chloride of $\alpha^{19°}_{5461}$ − 1·02° (*l*, 1) from which, on hydrolysis, alcohol of $\alpha^{19°}_{5461}$ − 0·08° (*l*, 1) was obtained.

The alcohols obtained from αγ-dimethylallyl chloride did not change in rotatory power when kept for many months, and their rotatory power is not very sensitive to temperature; *e.g.*, a specimen had $\alpha^{12°}_{5461}$ + 1·45°, $\alpha^{24°}_{5461}$ + 1·56°, whereas (+)-αγ-dimethylallyl alcohol has $\alpha^{18°}_{5461}$ + 2·00°, $\alpha^{24°}_{5461}$ +0·65° (*l*, 2). The rotatory powers of the two alcohols are affected in the opposite sense by temperature.

Derivatives of the Alcohol obtained by Hydrolysis of αγ-Dimethylallyl Chloride.—(i) *Hydrogen phthalate.* A number of preparations were made (*e.g.*, from the alcohols in the last double column of foregoing table) by the usual method, with phthalic anhydride and pyridine (Hills, Kenyon, and Phillips, *loc. cit.*). The phthalate did not crystallise well. Some preparations were extracted with carbon disulphide [in which the (+)- and (−)-phthalates are more soluble than the *dl*-]; others were dissolved in ethyl alcohol or in chloroform. All the solutions were optically inactive in the visible spectrum.

(ii) p-*Nitrobenzoate.* This (4·3 g.) was obtained from the alcohol (1·7 g.), α_{5461} + 1·46° (*l*, 2), by Einhorn's method. The crude ester (m. p. 52—54°) was optically inactive in ethyl alcohol (*c*, 10·0; *l*, 2); after recrystallisation from aqueous alcohol it had m. p. 56°, alone or mixed with authentic *dl*-αγ-dimethylallyl *p*-nitrobenzoate.

(iii) *Acetate.* The alcohol (3 g.), $\alpha^{20°}_{5893}$ + 1·20°, $\alpha^{20°}_{5461}$ + 1·49°, $\alpha^{20°}_{4358}$ + 2·55° (*l*, 2), was mixed with pyridine (3·5 g.) and acetic anhydride (4·2 g.). The rotatory power of the solution (α_{5461} + 0·60°; *l*, 2) did not change during 2 days; the mixture was then warmed for 2 hours on the steam-bath, dissolved in ether, and the solution washed, dried, and distilled. On redistillation, the acetate had b. p. 136—137°, $n^{19°}_{5893}$ 1·4179, $\alpha^{18°}_{5893}$ + 0·29°, $\alpha^{18°}_{5780}$ + 0·31°, $\alpha^{18°}_{5461}$ + 0·33°, $\alpha^{18°}_{4358}$ + 0·55° (*l*, 0·5).

(iv) *Benzoate.* Prepared by Einhorn's method from alcohol (3 g.) with $\alpha^{20°}_{5893}$ + 1·20°, $\alpha^{20°}_{5780}$ + 1·34°, $\alpha^{20°}_{5461}$ + 1·49°, $\alpha^{20°}_{4358}$ + 2·55° (*l*, 2), 5·5 g. of *dl*-benzoate were obtained after redistillation; b. p. 140°/21 mm., $n^{23°}_{5893}$ 1·5075. From alcohol with $\alpha^{21°}_{5893}$ + 0·05°, $\alpha^{21°}_{5461}$ + 0·09°, $\alpha^{21°}_{4358}$ + 0·16° (*l*, 0·5), the benzoate had b. p. 124°/13 mm., $\alpha^{16°}_{5893}$ − 0·04°, $\alpha^{16°}_{5461}$ − 0·06°, $\alpha^{16°}_{4358}$ − 0·17° (*l*, 0·5). From alcohol with $\alpha^{19°}_{5893}$ − 0·16°, $\alpha^{19°}_{5461}$ − 0·11° (*l*, 0·5), the benzoate had b. p. 126°/14 mm., $n^{16°}_{5893}$ 1·5084, $\alpha^{16°}_{5893}$ + 0·10°, $\alpha^{16°}_{5461}$ + 0·14°, $\alpha^{16°}_{4358}$ + 0·42° (*l*, 0·5). The same specimen of alcohol gave an optically inactive hydrogen phthalate.

(v) *Reduction to methyl-*n*-propylcarbinol.* The alcohol ($\alpha^{17°}_{5893}$ + 1·50°, $\alpha^{17°}_{5461}$ + 1·66°, $\alpha^{17°}_{4358}$ + 2·9°; *l*, 2) absorbed the theoretical amount of hydrogen within 5 mins. in presence of Adams's platinum oxide catalyst. The resulting methyl-*n*-propylcarbinol had b. p. 118°, $n^{17·5°}_{5893}$ 1·4061, $\alpha^{18°}_{5893}$ − 0·15° (*l*, 0·5). Pickard and Kenyon (J., 1911, **99**, 49) give $\alpha^{20°}_{5893}$ + 11·10° (*l*, 1) for the optically pure carbinol.

Partially Racemised Derivatives prepared from the (+)Alcohol which has undergone Mutarotation.—(i) *Hydrogen phthalate.* See Hills, Kenyon, and Phillips (*loc. cit.*).

(ii) *Benzoate.* A specimen of the (+)alcohol, with $\alpha^{14°}_{5461}$ + 1·76° (*l*, 2) when freshly prepared, had $\alpha^{21°}_{5461}$ − 7·03° (*l*, 2) after 18 months. It was then converted into the benzoate (Einhorn's method), which had b. p. 137—138°/18 mm., $n^{22°}_{5893}$ 1·5078, $\alpha^{24°}_{5893}$ + 7·38°, $\alpha^{24°}_{5780}$ + 7·97°, $\alpha^{24°}_{5461}$ + 9·41°, $\alpha^{24°}_{4358}$ + 21·00° (*l*, 0·5).

(iii) *Methyl-n-propylcarbinol.* αγ-Dimethylallyl alcohol having $\alpha^{20°}_{5461}$ − 0·16° (*l*, 2) 15 months after its preparation from the (+)phthalate was reduced in the presence of platinum oxide to methyl-*n*-propylcarbinol, b. p. 117—118°, $n^{14·5°}_{5893}$ 1·4077, $\alpha^{17°}_{5893}$ + 5·02°, $\alpha^{17°}_{5780}$ + 5·22°, $\alpha^{17°}_{5461}$ 5·89°, $\alpha^{17°}_{4358}$ + 9·7° (*l*, 0·5).

αγ-Dimethylallyl phenylurethane was prepared by mixing the alcohol (2 mols.) and phenylcarbimide (1 mol.) and after 5 days at room temperature removing the excess of alcohol by distillation under reduced pressure (b. p. 35°/12 mm.), the alcohol then being redistilled at atmospheric pressure; the residual urethane either crystallised (in a mass of fine, oblong needles, very soluble in light petroleum) or was isolated by distillation. (i) From the (−)alcohol with $\alpha^{19°}_{5893}$ − 0·05°, $\alpha^{19°}_{5461}$ − 0·10°, $\alpha^{19°}_{4358}$ − 0·56° (*l*, 0·5), the recovered alcohol had b. p. 120—122°, $n^{18·5°}_{5893}$ 1·4309, $\alpha^{19°}_{5893}$ + 0·04°, $\alpha^{19°}_{5461}$ + 0·16°, $\alpha^{19°}_{4358}$ + 0·35° (*l*, 0·5).

(ii) From the (+)alcohol, which 7 weeks after its separation from the phthalate had $\alpha^{17°}_{5461}$ + 1·46° (*l*, 2), the recovered alcohol had $\alpha^{13°}_{5461}$ + 1·84° (*l*, 2) which, by calculation from figures given by Hills, Kenyon, and Phillips (*loc. cit.*), corresponds to $\alpha^{17°}_{5461}$ + 1·41°. After redistillation the alcohol had b. p. 119·5—120°, $\alpha^{16°}_{5893}$ + 0·57°, $\alpha^{16°}_{5461}$ + 1·00°, $\alpha^{16°}_{4358}$ + 4·00° (*l*, 2), and 118 days after redistillation, $\alpha^{21°}_{5893}$ − 0·78°, $\alpha^{21°}_{5461}$ − 0·63°, $\alpha^{21°}_{4358}$ + 0·80° (*l*, 2). The urethane crystallised, m. p. 32°, $[\alpha]^{20°}_{5893}$ − 72·6°, $[\alpha]^{20°}_{5780}$ − 76·5°, $[\alpha]^{20°}_{5461}$ − 87·9°, $[\alpha]^{20°}_{4358}$ − 162·5° in carbon disulphide (*l*, 2) (*c*, 5·28) (Found: N, 6·8. $C_{12}H_{15}O_2N$ requires N, 6·8%).

(iii) From *lævo-αγ*-dimethylallyl alcohol (obtained from hydrogen phthalate of $[\alpha]^{20°}_{5461}$ − 15·7° in chloroform). The original alcohol had $\alpha^{20°}_{5893}$ − 0·20°, $\alpha^{20°}_{5461}$ − 0·38°, $\alpha^{20°}_{4358}$ − 1·63° (*l*, 2) and the recovered alcohol had $n^{20°}_{5893}$ 1·4279, $\alpha^{20°}_{5893}$ + 0·05°, $\alpha^{20°}_{5461}$ + 0·08°, $\alpha^{20°}_{4358}$ + 0·22° (*l*, 0·5); it gave a hydrogen phthalate with $[\alpha]^{20°}_{5893}$ − 12·6°, $[\alpha]^{20°}_{5461}$ − 16·8°, $[\alpha]^{20°}_{4358}$ − 39·7° in chloroform. The urethane crystallised with difficulty; it had $n^{20°}_{5893}$ 1·5422 (supercooled), $[\alpha]^{20°}_{5893}$ + 2·5°, $[\alpha]^{20°}_{5461}$ + 3·2°, $[\alpha]^{20°}_{4358}$ + 11·4° (*l*, 0·5; *c*, 10·4 in ethyl alcohol) (Found: N, 6·6%).

(iv) (+)Alcohol, which originally had $\alpha^{20°}_{5893}$ + 0·23°, $\alpha^{20°}_{5461}$ + 0·46°, $\alpha^{20°}_{4358}$ + 1·82° (*l*, 1), had after 201 days $\alpha^{17°}_{5893}$ − 0·43°, $\alpha^{17°}_{5461}$ − 0·38°, $\alpha^{17°}_{4358}$ + 0·49° (*l*, 2) and was then converted into the urethane. The residual alcohol had $\alpha^{20°}_{5893}$ − 0·42°, $\alpha^{20°}_{5461}$ − 0·36°, $\alpha^{20°}_{4358}$ − 0·25°, (*l*, 0·25) and gave a hydrogen phthalate with $[\alpha]^{20°}_{5893}$ + 18·5°, $[\alpha]^{20°}_{5461}$ + 24·5°, $[\alpha]^{20°}_{4358}$ + 52·5° (*l*, 2; *c*, 4·15 in chloroform). The urethane (b. p. 174°/18 mm.) had $\alpha^{20°}_{5893}$ − 6·02°, $\alpha^{20°}_{5461}$ − 7·40° (*l*, 0·5; homogeneous) and $[\alpha]^{20°}_{5893}$ − 3·3°, $[\alpha]^{20°}_{5461}$ − 4·3° (*l*, 0·5; *c*, 10 in ethyl alcohol) (Found: C, 70·9; H, 7·7. $C_{12}H_{15}O_2N$ requires C, 70·0; H, 7·5%).

Presence of Peroxides in Old Samples of the Alcohol.—A year after preparation from the phthalate, samples of αγ-dimethylallyl alcohol gave positive reactions for peroxides by the method of Kharasch and Mayo (*J. Amer. Chem. Soc.*, 1933, **55**, 2468), but addition of 0·2% of the pro-oxygen benzoyl peroxide, or the anti-oxygen diphenylamine, did not affect the rate of mutarotation of the (+)alcohol.

Attempts to Isolate an Optically Active Acid Fraction from αγ-Dimethylallyl Alcohol.—A number of specimens of the alcohol which had undergone mutarotation were dissolved in ethyl ether and washed with aqueous alkalis; the washings were in all cases optically inactive.

α-Naphthylurethane of αγ-Dimethylallyl Alcohol.—Levene and Haller (*loc. cit.*) obtained the urethane prepared from the *dextro*-alcohol in two fractions, m. p. 109—113° and 130° severally; the latter had the higher rotatory power. We find the *dl*-urethane from alcohol freshly prepared from the hydrogen phthalate to have m. p. 105°.

α-Naphthylurethane of dl-*Methylallylcarbinol.*—The urethane obtained by combination of the carbimide (2 g.) and the alcohol (1 g.) at room temperature was extracted with hot *cyclo*hexane. The extract deposited two types of crystal, bulky clusters of soft needles, m. p. 46—47°, and hard glassy tablets, m. p. 62° (Found: N, 5·4. Calc. for $C_{10}H_{17}O_2N$: N, 5·5%). These could be separated by the readier solubility of the former in hot light petroleum, but recrystallisation of either form from petroleum gave a mixture of both. It would appear, therefore, that they are isomorphous forms of the same compound. Levene and Haller (*J. Biol. Chem.*, 1929, **81**, 425) give 47—49° as the m. p. of the urethane prepared from *lævo*-carbinol.

Attempts to Fractionate the α-Naphthylurethane of αγ-Dimethylallyl Alcohol.—A specimen of the *dl*-alcohol which had been stored for 18 months was taken to represent alcohol which had undergone mutarotation. It gave a urethane of m. p. 105° after recrystallisation, and no fraction of lower m. p. could be isolated from the mother-liquors.

α-Naphthylurethane of the Alcohol prepared by Hydrolysis of dl-*αγ-Dimethylallyl Chloride.*—The alcohol (14·3 g., b. p. 118—120°) readily combined with α-naphthylcarbimide (29 g.). The resultant solid was extracted several times with boiling ether (200 c.c.), and the extract evaporated to about 50 c.c., yielding αγ-dimethylallyl naphthylurethane (13·5 g.), m. p. 98—101° raised to m. p. and mixed m. p. 105° by one recrystallisation. The filtrate from the crude urethane was evaporated to dryness, the crystalline residue extracted with boiling light petroleum (40 c.c.), and the extract allowed to evaporate at room temperature until its volume was about 5 c.c.; the crystalline crop of rosettes of short needles had m. p. 98—100°. The filtrate was allowed to evaporate down to about 1 c.c., and the crystalline crop of needles showed no signs of softening until 92° and had m. p. 92—97°.

Fractional Distillation of the Alcohol obtained from αγ-Dimethylallyl Chloride.—Alcohol obtained from *dl*-chloride by the above method was separated by slow distillation into the following fractions: b. p. 80—115° (1 c.c.); 118—122° (14 c.c.); 124—129° (1 c.c.); 130—160° (0·5 c.c.).

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92. *The Heat of Adsorption of Ethyl Chloride and of Sulphur Dioxide on Sugar Charcoal.*

By S. JOHN GREGG.

The heats of adsorption were measured by a Bunsen ice calorimeter, and the adsorption isotherms determined, from very low pressures up to atmospheric for sulphur dioxide and up to the saturated vapour pressure for ethyl chloride, by a volumetric method.

The chief feature of the results was a sharp fall in the differential heat of adsorption of ethyl chloride, from about 11,500 cals./mole to near the latent heat of condensation 6,000 cals./mole, occurring within a narrow adsorption range and at pressures less than one-quarter of the saturated vapour pressure. The effect is ascribed

to the inception of a layer more than one molecule thick. Henry's law was not obeyed by either gas even at the lowest pressures studied, probably because the film was still not sufficiently dilute to behave as a perfect two-dimensional gas.

In preliminary experiments the differential heat of adsorption of ethyl chloride on charcoal was found to fall, within a narrow adsorption range and at pressures considerably below the saturated vapour pressure p_s, from some 12,000 cals./mole to near the latent heat of condensation, 6,000 cals./mole. Since the effect seemed to indicate a transition from a unimolecular to a thicker adsorbed layer, it was decided to investigate the system more fully by determining the adsorption isotherm from very low pressures up to p_s, and simultaneously measuring the heat of adsorption calorimetrically. The system sulphur dioxide–charcoal (where, it was anticipated, the behaviour would be simpler) was selected as a control.

Experimental.

Materials.—To minimise the well-known disturbing effects of mineral impurities, sugar charcoal—made by heating B.D.H. "Analytical Reagent" sucrose for 1½ hrs. in a silica tube in an electric furnace at 550°—was used as adsorbent. It was activated by passing over it a stream of air, at 0·8 l./hr., whilst heated to 720° in a silica tray in a tubular electric furnace for 6 hrs.; it was then sieved through 180 mesh. Since the sucrose is specified to contain $\pm 0{\cdot}02\%$ of mineral matter, the ash content of the charcoal should not exceed 0·04%.

The sulphur dioxide from a syphon was redistilled in a high vacuum, and the middle fraction only retained. The ethyl chloride (B.D.H. pure) was passed in succession through traps cooled severally to −60°, −110°, and −182°; the −110° condensate was fractionally redistilled in a high vacuum, and the middle fraction alone retained. The vapour pressures of each gas agreed at a number of temperatures with the values from Landolt and Börnstein's Tables within ±1%.

Procedure.—The usual volumetric method was used, successive measured volumes of gas at known pressure and temperature being admitted from a gas burette into the dead space in contact with the charcoal, or withdrawn therefrom into a vessel of known volume, the quantity adsorbed being obtained as the difference between the sum of the amounts admitted and the amount remaining unadsorbed in the dead space. The apparatus was all-glass (Monax) with mercury cut-offs to control the movement of gas. Dead-space pressures exceeding some 0·5 cm. were read on an ordinary mercury manometer with wide limbs (*ca.* 1·2 cm. diam.), and lower pressures on a three-stage McLeod gauge. All levels were read by an accurate cathetometer, and the deviations of the gases from Boyle's law were corrected for in all calculations.

The heat, q, evolved by each increment in the amount adsorbed was measured by having the charcoal bulb enclosed in the inner tube of a Bunsen ice calorimeter, the intermediate space being filled with mercury to promote thermal conduction from charcoal to ice sheath. The change in volume of the sheath (and thus q) was obtained in terms of the change in weight of a tared crucible containing mercury, into which the ground-off end of the capillary of the calorimeter dipped. In order to minimise thermal errors due to expansion or compression after leaving the burette, the gas was made to pass through a worm coil immersed in a water-bath at a known temperature immediately before entering the adsorption bulb.

To carry out a run, the charcoal, contained in the adsorption bulb which had been previously fused on to the apparatus (blowing being through a phosphoric oxide tube), was out-gassed for several days, usually at 250°, till the dead space pressure was *ca.* 10^{-6} mm. It was then cooled, sulphur dioxide or ethyl chloride admitted up to a dead-space pressure of some 5 cm., and left to stand for some hours, being finally out-gassed, first at room temperature and then at a higher temperature, usually 150°. When the pressure had again fallen to *ca.* 10^{-6} mm., the heater was removed, and the connection to the pumps closed when the charcoal had cooled to room temperature; pressure was now unreadable. (This "flushing-out" technique is recommended by Burrage, *J. Physical Chem.*, 1933, **37**, 510, 735.) The calorimeter was now raised into position, and when after an hour or so the calorimeter showed a steady rate of drift, the first charge of gas was admitted from the burette. Readings of the presssure and weighings of the crucible were taken at intervals till the former was nearly or quite constant. This equilibrium was never completed in less than an hour and often required much longer (see detailed results).

Results.—Let q_2 cals. be the heat evolved when the number of c.c. (at N.T.P.) adsorbed by the w g. of charcoal increases from wx_1 to wx_2 (after correction for the heat given up by $wx_2 - wx_1$ c.c. in cooling from room temperature to 0°); then the approximate differential heat of adsorption ΔH_2 for the adsorption range wx_1 to wx_2 is given by $\Delta H_2 = q_2 \times 22414/w(x_2 - x_1)$ cals. per mole of gas. Results are recorded, in Figs. 1 and 2, as a plot of x the adsorption in c.c. (at N.T.P.) per *gram* of charcoal—against $\log_{10} p$, where p is the equilibrium dead-space pressure in cm. of murcury; and also as a plot of ΔH_2 against the corresponding average value of x, *viz.*, $(x_1 + x_2)/2$. Experimental points are numbered in the order in which they were determined. The lines in Fig. 2 and the upper part of Fig. 1 merely join related points and do not necessarily indicate the best curve. The main source of error in q is the "drift" in the calorimeter, *i.e.*, the change in weight of the mercury due to thermal leaks between the calorimeter and its surroundings, and possibly also to a slow alteration in the volume of the calorimeter itself. To minimise the drift the water was boiled out under reduced pressure *in situ* before forming the ice sheath, the ice in the outer ice bath (a large thermos flask) was made from distilled water and was constantly stirred, and the calorimeter, which had its own vacuum jacket fused on, was made small—12 cm. long by 5 cm. outside diameter—and of Pyrex glass in order to reduce volume changes due to elastic after-working of the glass. These measures did not entirely eliminate the drift, however, and it had to be determined before (B) and after (A) each measurement of q, the calculated drift for the duration of the measurement (based on the average of A and B) being subtracted from the total change in the weight of the mercury. Sometimes A and B differed considerably, and this led to some uncertainty in the value of q. The percentage error from this source is greater where the increments Δx are small, as is often the case at the higher pressures; this error varies from about ±1% for the best cases to 5—10% for the worst. Although undesirably large, the error could be reduced only by increasing the values of Δx, *i.e.*, by spacing the experimental points more widely; but this would no longer have given even an approximation to the differential heat of adsorption in those ranges where this quantity varied rapidly with x, *i.e.*, in exactly those regions which it was desired to study most closely.

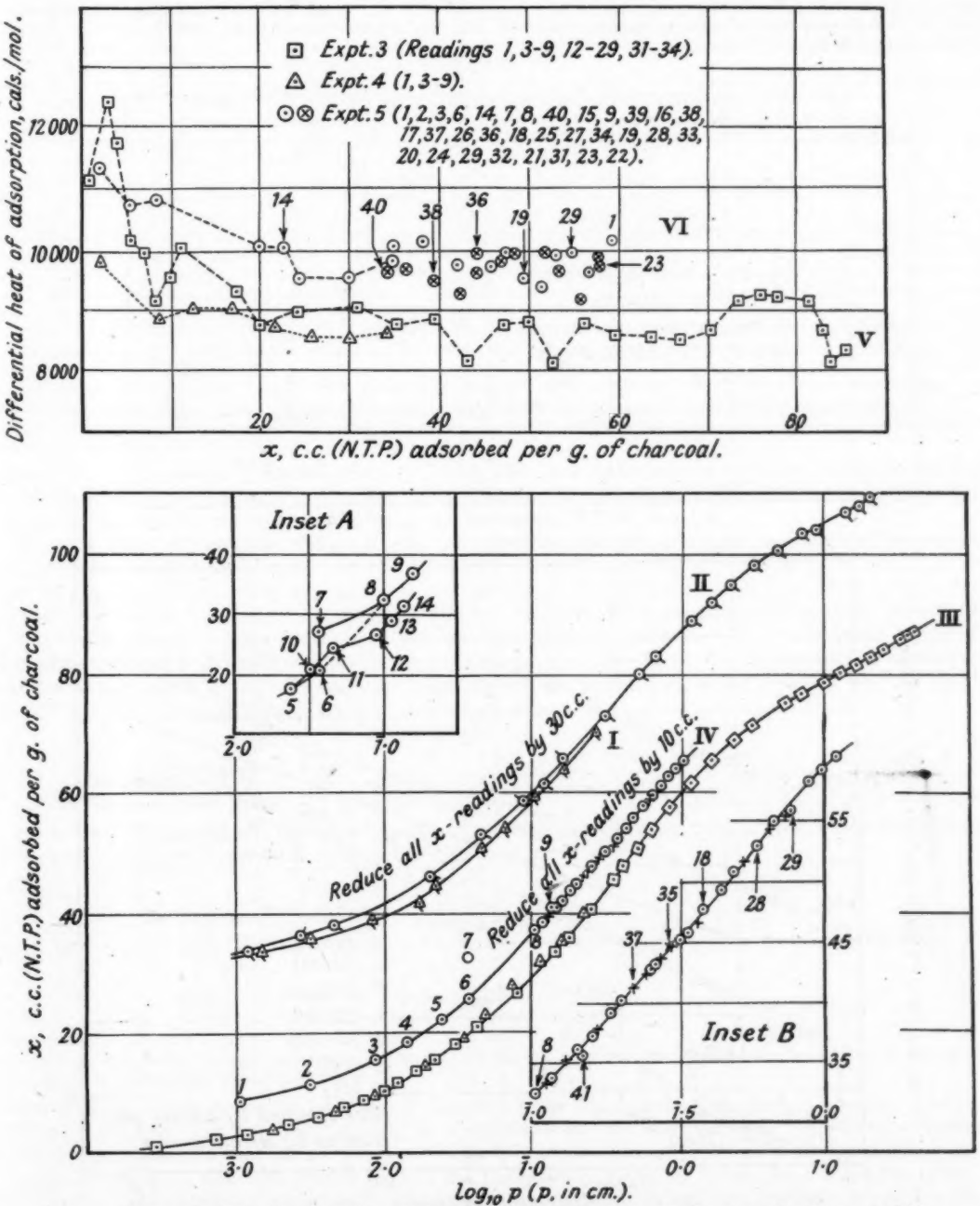
Experiments with sulphur dioxide. Expt. 1. (Fig. 1, Curve I.) 1·076 G. of charcoal. Out-gassed at 250°. Equilibration 1½—2 hrs. No heat measurements.

Expt. 2. (Fig. 1, Curve II.) At the end of Expt. 1 the charcoal was out-gassed at 250°, whereupon owing to a breakage some air entered and remained for some hours in contact with the hot charcoal. This probably altered its state of activation slightly. After repair, the charcoal was out-gassed and flushed out. Equilibration 1½—2 hrs. No heat measurements.

Expt. 3. (Fig. 1, Curves III and V.) Fresh sample of charcoal (3·80 g.). Out-gassed at 190°, and flushed out. Equilibration 1½—2 hrs. Probable error in ΔH usually ± 2 to $\pm 3\%$ but *ca.* $\pm 6\%$ in readings 3, 4, 7, 18, 28, 29, 31, 34.

Expt. 4. (Fig. 1, Curves III and V.) At the end of Expt. 1 some air entered. The charcoal was then out-gassed first at 15° then at 190°, but not flushed out. Probably error in ΔH, $\pm 1\%$ to $\pm 2\%$. Equilibration 1—2 hrs. The

FIG. 1.



△ Expt. 1 (Readings 1-12); ⊙ Expt. 2 (Readings 1-23); ⊡ Expt. 3 (Readings 1-36);
△ Expt. 4 (Readings 1-10); ⊙⊗ Expt. 5 (Order of readings after 7 is 8; 40, 14, 39, 15, 41; 9, 38, 43, 16, 37; 25, 44, 17, 36, 35; 46, 26, 45, 34, 18, 23, 27, 19, 24, 28; 22, 20, 23, 31, 29; 21, 30, 22).
⊙ Obtained by adding gas. ⊗ Obtained by withdrawing gas.

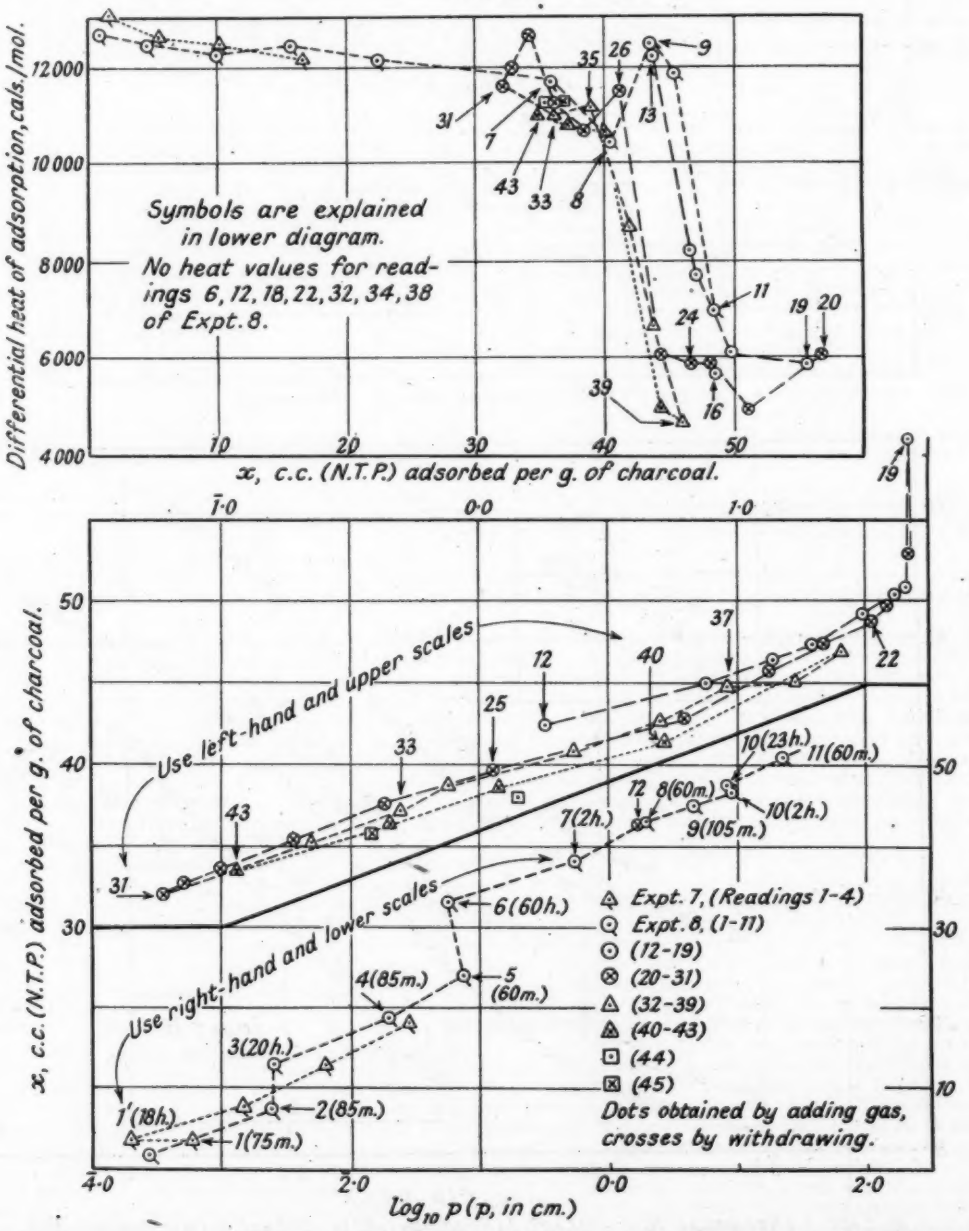
semilog isotherm points fall on exactly the same curve as those of Expt. 3, but the heat curve for Expt. 4 lies slightly above that for Expt. 3.

Expt. 5. (Fig. 1, Curves IV and VI.) At the end of Expt. 4 some air entered and remained for some hours in contact with the charcoal at 15°. Out-gassed at 15°, then at 190°, and flushed out. Equilibration 1—2 hrs. Probable error in ΔH is ± 1 to $\pm 2\%$ except reading (22), 3%; (33), 4%; (36), 7%.

In the region (6) to (9) the semilog isotherm showed anomalous behaviour (see Inset *A*). After (9), gas was accordingly withdrawn by pumping till p fell to a certain value [given by $\log p = \bar{2}{\cdot}412$, point (10)] below the abnormal region, to find if, on re-adsorption, the abnormality could be reproduced [see points (10), (11), (12), (13), . . .; point (10) was interpolated on to the curve (4)—(5)—(6)]. From Inset *A* it will be seen that, though the re-adsorption curve still exhibits some irregularity, the original feature is not exactly reproduced, and it remains undecided whether the effect is real or arises from an unsuspected experimental error.

To connect the remainder of the re-adsorption curve [points (14) . . . , see Curve IV and Inset B] with the earlier part [(1) . . . (10)], point (14) was interpolated between (8) and (9); a small but constant uncertainty (<4 c.c.) therefore attaches to all points from (14) onwards.

FIG. 2.



Though in this experiment gas was added and withdrawn in arbitrary order (see numbering of points), "both adsorption increasing" and "adsorption decreasing" points lie on the same curve within experimental limits, proving hysteresis to be sensibly absent.

Expt. 6. New sample of charcoal. Out-gassed at 250° and flushed out. This was a low-pressure experiment to test Henry's law. No heat measurements.

In all the three sulphur dioxide experiments for which heat data were obtained, it is seen (Fig. 1) that, as x increases from zero, ΔH at first falls somewhat, then remains fairly constant over a considerable range of x; ΔH does not show the continual fall which is perhaps more usual (cf. McBain, "Sorption of Gases by Solids," 1932, Chap. XIV). It may increase slightly and then diminish at high values of x (see Curve V), but experimental error is rather large here.

Experiments with ethyl chloride. Expt. 7. (Fig. 2.) New sample of charcoal (3·72 g.). Out-gassed at 250°, and flushed out.

Expt. 8. (Fig. 2.) After four points of Expt. 7 had been taken, the system was out-gassed at 15° and left for four weeks; it was then flushed out with ethyl chloride and out-gassed at 150°. At all pressures, but particularly at <0·1 mm., there was extensive " drift " in both Expts. 7 and 8; *e.g.*, the pressure always fell appreciably on standing overnight [cf. points (1) and (1′) of Expt. 7]. Owing to the impracticability of extending calorimetric measurements over many hours, and since ΔH determinations were the primary object of the experiment, the next addition of gas was usually made after 1—2 hrs. [the actual times for points (1) to (11) are given in Fig. 2] even though pressure was still falling; consequently, the isotherm curve does not quite correspond to equilibrium conditions, though the deviation therefrom is much less at the right-hand than at the left-hand end.

Owing to a manipulative error at point (12), there is a small uncertainty, not exceeding 3 c.c., in the position of the semilog isotherm subsequent to point (12). Its general shape, and the values of ΔH, are unaffected.

Calorimetric errors are very variable, being much greater at higher pressures where Δx, and therefore Δq, at each reading is small. For small adsorptions the probable error in ΔH is ± 2 to $\pm 3\%$, increasing to as much as ± 5 to $\pm 10\%$ for the larger adsorptions where p is approaching p_s.

The fall in ΔH as x increases from zero, already noted for sulphur dioxide, is less marked with ethyl chloride; the data for intermediate adsorptions (say 10—30 c.c.) are too scanty to say whether ΔH remains constant within experimental error or decreases slightly. The most striking feature of the ethyl chloride results, however, is the relatively sudden fall in ΔH from about 11,500 cals./mole to near the latent heat of condensation, 6000 cals./mole, occurring within a narrow range of x [the low values of (21), (39), and (40) are probably due to experimental error]. The fall occurred on five runs, three with adsorption increasing and two with adsorption decreasing [see (10)—(11), ⊙; (13)—(14)—(15)—(16), ⊙; (24)—(25)—(26)—(27), ⊗; (33)—(35)—(36)—(37)—(39), △; (39)—(40)—(41)—(42), ▲] and there can be no doubt as to the reality of the effect. It occurred at pressures of the order of 10 cm., *i.e.*, considerably below the saturated vapour pressure, *viz.*, 46·9 cm. Owing to the experimental necessity of having finite values of Δx there is an uncertainty of some 3 c.c. as to the exact value of x (say x_s) at which the fall commences; but it seems clear that x_s varies somewhat from one run to another.

Curves drawn through the " adsorption increasing points " (13)—(20) and the " adsorption decreasing " points (21)—(32) respectively do not coincide, the difference being slightly but definitely greater than experimental error. This lack of coincidence is not ordinary adsorption hysteresis, however, for the value of x at a given p value is *less* on the " decreasing " than on the " increasing " curve, not greater.

Discussion.—In an earlier communication (J., 1942, 696) reasons have been advanced for the belief that the fall in the differential heat of adsorption just noted denotes the completion of a monolayer of ethyl chloride and the inception of a thicker layer.

In the same paper it was also explained how, by measuring the area under the semilog isotherm from zero pressure up to a given pressure p, the values of FA and FS corresponding to p can be obtained (F = surface pressure of adsorbed film; A = area occupied per molecule of adsorbate; S = area of adsorbent per g.); and FA–FS curves are there given for Expts. 3 and 8. In Expt. 3 the experimental readings extend to very low pressures, so the summation from zero pressure is particularly accurate. The remaining sulphur dioxide experiments all give FA–FS curves of the same general shape as does Expt. 3. The reciprocal of the slope of the rectilinear portion of the FA–FS curve gives the monolayer capacity x_0 of the charcoal, *i.e.*, the number of c.c. (N.T.P.) which can be adsorbed in a completed monolayer :

Expt. No.	2.	3.	5.	8.
x_0	113 ± 3 *	119 ± 3	136 ± 3	47 ± 2
Charcoal No.†	X b	X a	X c	XII b

* Erroneously given as 135 ± 3 in *loc. cit.*, p. 701. † Quoted in *loc. cit.*, p. 701.

Despite the fact that the readings extended to very low pressures, in no case did the relationship between x and p become accurately linear, as shown by the following data :

	Expt. 2.				Expt. 3.					
x	3·72	6·02	8·07	16·19	0·85	2·38	3·16	4·70	6·0	7·52
$p \times 10^3$	1·24	2·83	4·69	20·9	0·29	0·72	1·17	2·21	3·56	5·25
$(x/p) \times 10^{-3}$	3·02	2·14	1·74	0·78	2·96	3·3	2·7	2·14	1·69	1·22

	Expt. 6.				
wx	0·915	1·854	2·289	3·091	3·412
$p \times 10^3$	0·099	0·195	0·265	0·382	0·408
$(wx/p) \times 10^{-3}$	9·2	9·5	8·7	8·1	8·4

(w = about 3 g., exact weight unknown. Expts. 1, 4, and 5 give results very similar to Expts. 2 and 3. Ethyl chloride shows a much more rapid fall in x/p.)

The results are not, however, to be taken as disproving the widely held view that, in absence of impurities, all adsorption follows " Henry's law " $x = kp$ (k = constant) at very low pressures : application of the Gibbs adsorption equation shows that the isotherm can have this linear form only when the adsorped film is so dilute that it can behave as a two-dimensional perfect gas (Langmuir, *J. Amer. Chem. Soc.*, 1917, **39**, 1888). For surface films of fatty acids on water such behaviour is approached, though not reached, when the area per molecule is 4000 A.^{2} (Adam and Jessop, *Proc. Roy. Soc.*, 1926, *A*, **110**, 423), *i.e.*, some 200 times greater than the incompressible area per molecule. An equivalent dilution in the present films on charcoal, where $x_0 \simeq 125$ c.c., would be $x = 0{\cdot}6$ c.c.; and with an adsorbate like sulphur dioxide, with its considerable external field, it is likely therefore that obedience to the linear law would be found only at pressures lower than those studied in Expts. 1—5. It is satisfactory that in Expt. 6, where the film dilutions are rather higher, the deviations of x/p from constancy do not greatly exceed experimental error.

WASHINGTON SINGER LABORATORIES, UNIVERSITY COLLEGE, EXETER. [*Received, May 13th*, 1943.]

93. *The Course of Autoxidation Reactions in Polyisoprene and Allied Compounds. Part III. The Oxidation of Rubber in the Presence of Acetic Acid or Acetic Anhydride.*

By George F. Bloomfield.

Oxidation of rubber by oxygen in the presence of acetic anhydride leads to formation of highly oxygenated products containing a considerable proportion of acetoxyl groups. The residual unsaturation of the products of highest acetoxyl content, taken in conjunction with other analytical characteristics, indicates that three, rather than two, acetoxyl groups normally combine with each isoprene unit attacked. Although the bulk of the oxygen introduced is present in the form of acetoxyl groups, a portion occurs as carboxyl and carbonyl groups; also, whenever acetic acid is used (partly or wholly) in place of acetic anhydride, some free hydroxyl groups appear in the oxidised rubber. The proportions of carboxyl and carbonyl groups observed can be satisfactorily correlated with the extent of chain-scission occurring during the oxidation, the groups in question forming the new ends of the severed molecules. Hydrolysis of the acetylated products yields hydroxy-acids which readily undergo lactonic elimination of water.

Acetic anhydride and acetic acid can clearly act as auxiliary reagents in autoxidation reactions, and the detailed results obtained with rubber can be best accounted for on the basis of α-methylene peroxidation, followed by decay reactions involving incorporation of the auxiliary reagent as well as oxidative attack at the double bonds of the rubber.

Reference has been made in Part I (J., 1942, 121) to the facile oxidation which occurs when rubber is exposed to oxygen in presence of boiling acetic anhydride. It might at first be suspected that oxidation is here greatly facilitated by destruction of the natural inhibitors present in the rubber by the acid medium employed (cf. Bruson, Sebrell, and Vogt, *Ind. Eng. Chem.*, 1927, **19**, 1187), but if this were the sole explanation of this rapid oxidation, then a sample of rubber from which the antioxidants had been removed by acetone extraction * would be expected to undergo oxidation in a neutral or alkaline medium at a rate comparable with that observed in the acidic medium, although the course of the secondary reactions, and hence the final products of oxidation, might well be considerably different in view of the diverse influence of acid and alkali on the mode of decay of the hydroperoxide of *cyclo*hexene (cf. Part I).

Bloomfield and Farmer (*J. Soc. Chem. Ind.*, 1935, **54**, 125T) first observed that the oxidation of olefins by oxygen can be much accelerated by the presence of acetic acid or anhydride, and similar observations by other authors have since been reported. If in these reactions autoxidation proceeds by addition of oxygen at the unsaturated centres of rubber to give peroxide groups $\begin{matrix}-C-C-\\ \quad|\quad|\\ \quad O-O\end{matrix}$ according to the Engler–Bach hypothesis, it might be supposed that ultimately there would be formed partly or wholly acetylated diols by reason of the decay of the peroxides in the presence of acetic acid or acetic anhydride. If, however, oxidative attack is directed in the first place to the α-methylene carbon atoms instead of to the unsaturated centres, tri-, di-, or mono-acetylated triol groups may be expected to arise at each $CH_2{\cdot}C{:}C$ unit, as discussed in Part I.

The Oxidation Process.—At ordinary temperatures the oxidation of solid rubber took place quite slowly when the hydrocarbon was immersed in acetic anhydride or acetic acid, but at 120—140° oxidation proceeded rapidly and the products of oxidation were sufficiently degraded to dissolve in the hot acetic acid or anhydride, giving a resinous material which by submission to a suitable separative procedure (see Tables III and IV) could be resolved into various fractions of high oxygen content and of comparatively low molecular weight. The undissolved rubber, on the other hand, although somewhat softer than it was originally, was only slightly oxygenated and but little degraded. The reaction could be considerably accelerated by adding small proportions of organic or inorganic cobalt salts to the acid or anhydride medium, but no obvious change in the course of reaction attended these additions.

It was hoped to bring about more regulated oxidation, and so to obtain more graded oxidation products, by bringing the rubber to reaction in solution, but in fact no significant oxidation occurred unless rubber recovered from one of the above oxidations conducted in the presence of acetic anhydride or acetic acid, and so already slightly oxidised, was used in place of fresh rubber, or unless the oxidation was started, but not indefinitely continued, in a medium relatively poor in hydrocarbon solvent (p. 359). Even under these modified conditions oxidation did not proceed beyond the incorporation of a few units % of oxygen unless the solution was irradiated or an organic salt of cobalt was added as a catalyst. In the latter case reaction proceeded to an advanced stage, yielding highly oxygenated products which, for all oxidations conducted in the presence of acetic anhydride, were very similar to those obtained in the absence of a solvent for the rubber. When, however, oxidation was accelerated by irradiation the reaction appeared to pursue a somewhat different course, since then rather less than half of the combined oxygen was found in acetoxyl groups (see p. 360).

It was necessary before proceeding further with the examination of the oxidation products formed in presence of acetic acid or its anhydride to ensure that no serious part of the oxygenation of rubber arose by the direct addition of acetic acid at the ethylenic centres of the hydrocarbon (cf. addition of acetic or di- or trichloroacetic acid to amylene; Konovalov, *Z. physikal. Chem.*, 1888, **2**, 380; Nernst and Hohmann, *ibid.*, 1893, **11**, 352). Accordingly, samples of rubber were treated for many hours with boiling acetic anhydride and others with boiling acetic acid in an atmosphere of carefully purified nitrogen. Under these conditions no combination of the rubber with either reagent could be detected. Furthermore, when rubber was sealed in an

* In the following account, unless otherwise specifically indicated, the term *rubber* means acetone-extracted crepe rubber.

evacuated tube together with acetic anhydride and sufficient benzene to promote considerable dissolution of the rubber, it was recovered substantially unchanged even after many hours' heating at 140°.

The main features therefore of the reaction under consideration are: (1) Rubber takes up substantial amounts of oxygen in presence of acetic acid or anhydride, but reaction is very slow and restricted in character unless a temperature well above 100° is used; (2) the rubber becomes increasingly degraded as the oxygen content of the product rises; and (3) only a portion of the oxygen incorporated is in the form of acetoxyl groups, especially where the presence of a hydrocarbon diluent causes the acetic acid or anhydride to be in low concentration.

The Constitution of the Highly-degraded Products.—Further study of the major reaction products obtained severally by use of undiluted acetic anhydride and acetic acid at 120—140° (products A and P, p. 359) showed that acetoxyl contents as high as 50% could be obtained without entire removal of the unsaturation of the rubber; the magnitude of the acetoxyl contents in the acetic anhydride products arising at similar stages of oxygenation appeared to be mainly a function of the freedom of the anhydride from acetic acid and use of acetic acid alone gave products of lowest acetoxyl content.

The products were non-peroxidic, acid substances (containing titratable carboxyl groups) and for the most part showed a significant content of unesterified hydroxyl groups. The chief analytical characteristics are given in Table I (blank spaces represent undetermined values).

TABLE I.

Highly Oxidised Products.

Product.	Medium.	Catalyst.	OAc, % (corr.).*	CO_2H, % (corr.).*	OH, %.	I.V.	*M.*	Analysis, %. C.	H.	O (diff.).	O content (OAc + CO_2H + OH).
A(i)	Ac_2O	None	50·5	6·0	—	49	—	59·85	6·9	33·25	31·7
A(ii)	,,	,,	44·0	4·0	—	—	—	63·1	7·4	29·5	26·7
A(i)2	,,	,,	55·0 †	7·1 †	—	—	—	—	—	—	—
A(i)3	,,	,,	42·2	5·7	2·5(*ca.*)	80	—	64·0	6·9	29·1	29·3
A(i)5	,,	,,	44·1	8·0	nil	71	716	61·1	6·9	32·0	29·6
A(i)6	,,	$Co(NO_3)_2$	39·6	6·0	nil	77	1143	63·9	6·9	29·2	25·8
A(i)7	,,	,,	47·3	5·4	0·3	71	1215	62·7	6·9	30·4	29·8
A(i)8	$C_6H_6 + Ac_2O$	CoL_2 ‡	36·8	6·0	0·3	91	1361	61·8	7·2	31·0	24·6
A(i)9	$C_6H_5Cl + Ac_2O$	None	36·1	6·3	4·0	90	1161	63·9	7·0	29·1	27·9
P(i)	AcOH	,,	33·2	8·2	3·0	98	—	62·2	7·25	30·55	26·6
P(i)2	,,	,,	31·8	5·6	5·2	—	—	63·6	7·4	29·0	26·2
P(i)3	,,	,,	27·8	7·8	4·1	90·5	—	63·6	7·3	29·1	24·5

* For the significance of the correction applied to these figures, see p. 358.
† Uncorrected value. ‡ *I.e.*, cobalt linoleate.

There is a discrepancy (average 2·7%) between the total oxygen content of the products as determined by elementary analysis and by summation of the acetoxyl, carboxyl, and hydroxyl oxygen. This is to be expected, since the scission of polyisoprene chains at the double bonds by autoxidation reactions normally gives rise to carbonyl groupings (see Part I). Direct determination of the carbonyl content in two examples [A(i)5 and P(i)3] gave values (3·9 and 6·4%) which were actually in excess of this difference. In the determination of hydroxyl contents by the precision method of Bolland (*Trans. Inst. Rubber Ind.*, 1941, **16**, 267) the usual vigorous evolution of methane was accompanied by a progressive slow evolution of gas, possibly due to enolisation of carbonyl groups, and the hydroxyl contents in Table I have been derived by neglecting the slow reaction [A(i)3 excepted]. Most of the molecular weights shown are to be regarded as maximum values, since the solubility of the products in benzene decreased after a time, and only in the case of A(i)5 was it possible to determine the molecular weight immediately after preparation. Saponification of the acetylated materials under conditions excluding any possibility of further oxidation resulted in decomposition of the acetoxyl groups and formation of additional hydroxyl groups. In Table II are given analytical details for the saponification products of six of the materials listed in Table I.

TABLE II.

Composition of Saponification Products.

Products from which derived.	I.V.	OH, %.	CO_2H, %.	C, %.	H, %.	O, %.
A(i)3 (42·2% OAc)	112	18	8·1	68·3	7·5	24·2
A(i)5 (44·0% OAc)	124	12·4	11·6	66·4	7·6	26·0
A(i)7 (47·3% OAc)	114	20	8·2	67·5	7·6	24·9
A(i)9 (36·1% OAc)	167	13·5	8·5	68·8	7·8	23·4
P(i)2 (31·8% OAc)	—	11·0	7·3	67·1	7·4	25·5
P(i)3 (27·8% OAc)	143	11·7	9·9	69·4	7·8	22·8

The presence of many free hydroxyl groups in the saponified materials appears to lead to considerable dehydration, possibly by lactone formation (largely intramolecular) with the carboxyl groups already present: not only were the hydroxyl contents much lower than were to be expected, but titration of the acid groups gave satisfactorily sharp end-points only when the materials were treated with excess of alkali and back-titrated. The carboxyl contents of the hydroxy-acids were somewhat greater than those calculated from the apparent

carboxyl content of the parent acetylated substances, and this was to be expected, since it was not possible to determine the carboxyl contents of the latter with very high precision owing to the presence of readily hydrolysable acetoxyl groups. The discrepancy was not generally large and an appropriate correction has been applied to the carboxyl contents of the acetylated substances in Table I. The application of this correction also involved a small correction to the acetoxyl contents. The compositions of the saponified materials derived from products of high acetoxyl content are in fairly good agreement with those calculated from the composition of the parent acetylated materials on the assumption that lactonic elimination of water between the carboxyl groups and a corresponding proportion of the hydroxyl groups has occurred, but there is less agreement in the materials originally of lower acetoxyl content, owing possibly to some lactonisation already present between carboxyl groups and free hydroxyl groups in the acetylated material.

When an attempt was made to divert secondary reaction along a different route by the use of an alkaline auxiliary reagent (alcoholic potassium hydroxide) in place of the acid ones used before, no significant oxidation occurred at temperatures in the neighbourhood of 80—100°, and even at 140° only 3% of combined oxygen was introduced after 64 hours, but an oxidation conducted in the presence of pyridine proceeded to a more advanced stage represented by the combination of 8·6% of oxygen, of which, however, only one-third appeared in the form of hydroxyl, carbonyl, and carboxyl groups. As in the case of acid auxiliary reagents, considerable molecular degradation occurred.

Mechanism of the Reaction.—Before considering the acetoxyl content in relation to the residual unsaturation of the highly oxygenated products, it is necessary to take into account chain scission, since the extent of degradation occurring during oxidation is such that end-groups must constitute an appreciable part of the molecule. Indeed, the observed orders of magnitude of the carbonyl and carboxyl contents are just such as would be expected to characterise chain scission products of molecular weight 700—1000 in which the groupings in question are confined to the ends of chains.

The autoxidation reaction now under consideration differs from that described in Part I in being thermal rather than mainly photochemical in character. Hence the course followed (and this applies especially to secondary reaction) may be very different from that previously discussed. If it be *assumed*, however, that oxidation necessarily consists at the first stage of the absorption of molecular oxygen in giving not merely peroxide groups but hydroperoxide groups, and that the decomposition of these, instead of following the ordinary thermal or photochemical course, is directly influenced by the presence of an auxiliary reagent (acetic anhydride, etc.), it becomes possible to make important comparisons between the observed and the expected character of the reaction products. It is obvious that in any particular oxidation the participation of the auxiliary reagent may be belated or for one cause or another fall short of completeness, and in this case the secondary reactions will comprise both normal thermal peroxidic degradations and " influenced " degradations. Also it may reasonably be assumed, since there is as yet no evidence to the contrary in any recorded autoxidation, that the oxidising power of the peroxide groups expends itself primarily in attacking the unsaturated centres in the molecule where such are present, so giving rise to chain-scission. The normal molecular form of the reaction products may accordingly be expected to be some oxygenated and acetoxylated modification of (I), in which $n < 6$, in which the most probable points of hydroperoxidation are at the asterisked carbon atoms.

Some of the inner isoprene units in the small fragments of the original rubber chains will have escaped reaction altogether, others in the main will (as indicated in Part I) have passed in the presence of acetic anhydride into acetoxylated units containing in all probability the systems (II) or (III), or to some extent (especially where the oxidation is conducted in the presence of acetic acid) the systems (IV) or (V). There does indeed appear to be one free hydroxyl group for every two acetoxyl groups in the oxidation products of higher hydroxyl content as the figures below indicate:

Product	A(i)9	P(i)	P(i)2	P(i)3
OH equivalent of OAc content, %	10·4	9·6	9·2	8·0
Free OH content, %	4·0	3·0	5·2	4·1

In the most highly acetylated products the acetoxyl content can be related to the iodine value without any complication arising from the presence of free hydroxyl groups, and these products conform closely with the structural type represented by (I). For instance, a substance (VI) requires C, 60·0; H, 7·45; OAc, 47·8; CO,

(I.) $CO_2H{\cdot}CH_2{\cdot}[\overset{*}{C}H_2{\cdot}CMe{:}CH{\cdot}CH_2]_n{\cdot}\overset{*}{C}H_2{\cdot}COMe$ $-CH(OAc){\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH_2-$ (II.)

$-CH_2{\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH(OAc)-$ (III.) $-CH(OH){\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH_2-$ (IV.) $-CH_2{\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH(OH)-$ (V.)

$CO_2H{\cdot}CH_2{\cdot}[CH(OAc){\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH_2]_2{\cdot}[CH_2{\cdot}CMe{:}CH{\cdot}CH_2]_2{\cdot}CH_2{\cdot}COMe$ (VI.)

$CO_2H{\cdot}CH_2{\cdot}[CH_2{\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH_2]_3{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COMe$ (VII.)

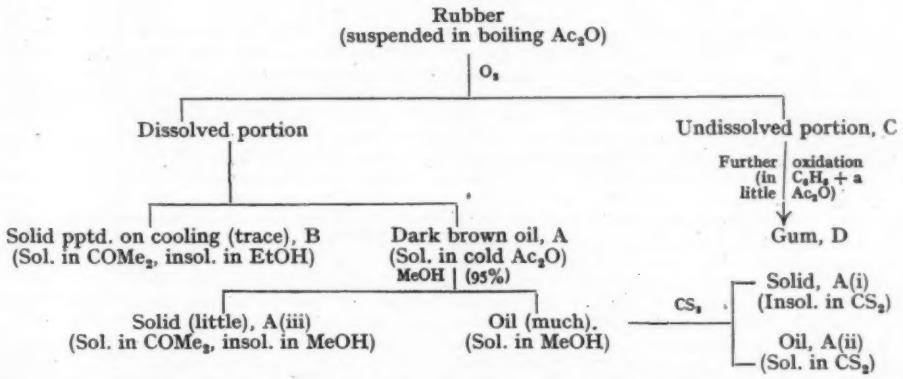
3·8; CO_2H, 6·1%; I. V., 69; *M*, 740 [cf. A(i)5 and A(i)7], whereas the alternative mode of distribution of the acetoxyl groups in a substance such as (VII), in which no α-methylene hydroperoxidation has taken place, so limiting the attachment of acetoxyl groups to two in each C_5H_8 unit attacked, would require a considerably lower iodine value (34) if the acetoxyl content is to remain the same.

Experimental.

Oxidation of Rubber in Boiling Acetic Acid or Acetic Anhydride.—The rubber (20 g.) was immersed in acetic acid or acetic anhydride (200 c.c.) which was boiled under reflux while a brisk stream of oxygen was bubbled through. The

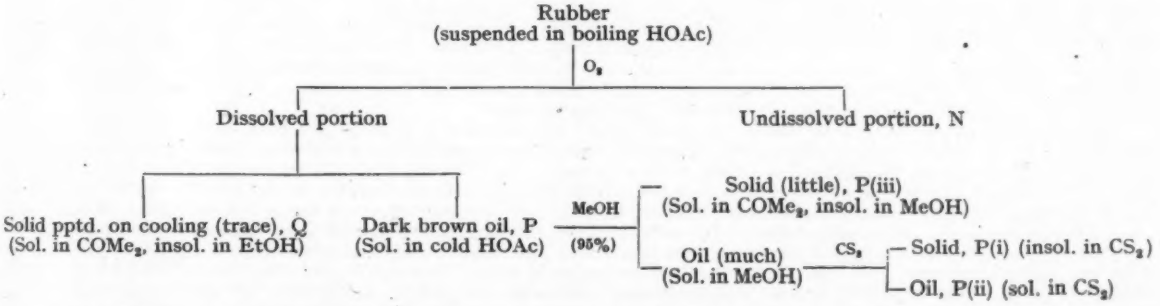
pieces of rubber disintegrated, and a portion dissolved giving a dark brown solution. After at least 20 hours' treatment the hot solution was decanted from a small amount of undissolved rubber. The solution, on cooling, desposited a little resinous matter. The material remaining in solution was isolated by evaporation of the acetic acid or anhydride under reduced pressure, the residue being submitted to the separative procedure indicated in Table III.

TABLE III.



In oxidations conducted in acetic anhydride, the yield of the brown solid product A(i) was about the same as that of the oil A(ii), the resinous products B and A(iii) being formed in relatively small amount. The solid A(i) softened at about 50° and melted to a gum at somewhat higher temperatures; a portion of the oil A(ii) was sufficiently degraded to be volatile at *ca.* 0·1 mm. pressure. When the oxidations were conducted in acetic acid, the amount of the corresponding products [solid P(i) and oil P(ii) : see Table IV] were reduced, and the oil P(ii) was formed in greater amount than the solid P(i).

TABLE IV.



When cobalt nitrate (0·4 g.) was added to the acetic acid or anhydride the amount of rubber dissolving in a comparable time was greater than in the absence of catalyst, but the products were very similar. The yield of the solid reaction product was, however, much greater than that of the oil, and in a typical experiment 29·6 g. of a solid reaction product [A(i)6] were obtained from 30 g. of rubber Complete removal of the cobalt salts from the reaction products presented much difficulty.

Oxidation of Rubber in Acetic Acid or Anhydride, using a Supplementary Solvent.—Oxygen was first led for 40 hours into a solution of rubber (10 g.) in benzene (500 c.c.) containing acetic anhydride (50 c.c.), a temperature of 80° being maintained. No significant degree of oxidation occurred. A similar result was obtained when an *iso*propyl acetate–acetic anhydride medium (at 90°) was used. When, however, a sample of the slightly degraded product C (Found : C, 88·0; H, 11·7%) was dissolved in benzene containing a little acetic anhydride, some evidence of oxidative attack became apparent after oxygen had been passed for 10 hours at 80°. The solution was then much less viscous, and removal of the solvent at this stage yielded a brown gum D, which was soluble in warm ethyl acetate, ether, hydrocarbon solvents, methyl ethyl ketone, and dioxan, but insoluble in alcohol or acetone (Found : C, 85·8; H, 11·6; OAc, *ca.* 2%).

Product D was soluble in a mixture of benzene (2 vols.) and acetic anhydride (1 vol.), but an oxidation of *rubber* attempted in this mixture proceeded only very slowly. When, however, the rubber (10 g.) was placed in a mixture of benzene (50 c.c.) and acetic anhydride (50 c.c.) and heated at 80° in contact with a stream of oxygen for 12 hours, and afterwards further benzene (50 c.c.) was added, then all of the rubber dissolved in the course of a further 8 hours' treatment with oxygen at 80°, so giving a solution of low viscosity. Removal of solvents gave a pale yellow, turbid gum behaving similarly to the material D towards solvents. When a solution of this new product in light petroleum (1000 c.c.) was allowed to stand, a pale yellow powder (0·2 g.) separated : this was removed by centrifuging and washed with light petroleum (Found : N, 9·4%). The resulting clear solution yielded on evaporation of the solvent a clear transparent pale yellow gum J {Found : C, 87·0; H, 11·8; N, nil; OAc, 0·86%; I. V., 353; intrinsic viscosity [η] (in benzene + 15% methanol), 0·244, from which M = 25,000}. In another oxidation conducted under similar conditions but using a mixture of equal volumes of acetic acid and anhydride a product K, very similar to J, was obtained {Found : C, 87·5; H, 11·95; OAc, 0·54%; I. V., 362; [η] (in benzene +15% methanol), 0·354, from which M = 36,000}, but when only acetic acid in admixture with the same proportion of benzene was used, a tacky, rubber-like substance L resulted {Found : C, 87·85; H, 11·9; OAc, nil; [η] (in benzene), 1·59, from which M = 95,000}.*

* The original rubber had M (by viscosity), *ca.* 300,000. These molecular weights have been determined by Dr. G. Gee, to whom the author's thanks are due.

Use of a Catalyst.—Oxidations were conducted under similar conditions to those described in the preceding paragraph with the addition of cobalt linoleate (0·2 g. per 10 g. of rubber). When a mixture of acetic acid, acetic anhydride, and benzene was treated with oxygen in the presence of this catalyst (at 80°) the product was very similar to that obtained from rubber, acetic anhydride, and oxygen at 140°. Like the latter product, it was divided into solid A(i)8 (10 g.) and liquid (3 g.) fractions which were respectively insoluble and soluble in carbon disulphide. Replacement of the acid-anhydride mixture by acetic acid alone led under the same conditions of oxidation to the formation of a less highly oxidised product, which by selective dissolution yielded the following fractions: alcohol–soluble portion, 3 g. (Found: C, 71·8; H, 9·2; OAc, 14·0; CO_2H, 4·0%); acetone-soluble portion, 3·0 g. (Found: C, 79·7; H, 10·4; OAc, 10·6; CO_2H, 1·5%); petroleum-soluble, acetone-insoluble portion, 3·6 g. (Found: C, 81·7; H, 10·9; OAc, 4·6%).

Oxidation in Presence of a Mutual (High-boiling) Solvent for the Reactants.—Rubber (10 g.) was swollen in chlorobenzene (100 c.c.), acetic anhydride (150 c.c.) added, and the mixture heated during 40 hours at 140° while a brisk current of oxygen was passed through. The separative procedure indicated in Table III was applied to the highly oxygenated product, and fractions severally soluble (oil, 5·4 g.) and insoluble [solid A(i) 9, 3·4 g.] in carbon disulphide were isolated. When the anhydride was replaced by acetic acid, the oxidation followed a different course and yielded a gum wholly soluble in light petroleum and in carbon disulphide, but insoluble in alcohol and in acetone.

Oxidation in Presence of Acetic Anhydride, with Irradiation.—A solution of acetic anhydride (25 c.c.) in benzene (50 c.c.) did not absorb oxygen when exposed at 30—40° in a Pyrex flask for 4 hours to ultra-violet light ("Hanovia" U.V.S. 500); moreover, the solution contained thereafter only a trace of peroxidic material. Accordingly, rubber (10 g.) in benzene (50 c.c.) and acetic anhydride (50 c.c.) was submitted to the action of oxygen at 80° until dissolved (cf. preceding experiments). Further benzene was then added, and the solution was oxidised at 30—40° under radiation as above for 16 hours. The solution, which had absorbed altogether 1,800 c.c. of oxygen, was concentrated under reduced pressure, and the gummy product isolated by pouring the concentrate into alcohol and removing the residual solvent in a high vacuum (Found: C, 68·2; H, 9·15; OAc, 20·0; peroxidic oxygen, *ca.* 1%; equiv., 2060; I. V., 210).

Saponification of Highly Acetylated Products.—To a solution of the acetylated material in the minimum quantity of 95% ethyl alcohol was added 2% aqueous sodium hydroxide (100 c.c. per g. of substance). The solution was boiled under reflux for 6 hours in an atmosphere of nitrogen, a little benzene being added to suppress frothing. The bulk of the solution was reduced considerably by evaporation under reduced pressure, and the remainder was acidified, whereupon the hydrolysis product was precipitated as a sludge, which was separated and washed on the centrifuge. In the later stages of washing the product readily passed into colloidal solution in water unless a few drops of a dilute acid were added. The product was rapidly dried at room temperature and reduced pressure, redissolved in alcohol, and separated from silica. The alcohol was finally removed at room temperature, yielding a friable solid, insoluble in hydrocarbons, readily soluble in alcohol, acetone, acetic acid, and pyridine. The yield was almost quantitative provided that care were exercised to prevent losses while washing the precipitate.

Oxidation in the Presence of Chloroacetic Acid.—The rubber (20 g.) was placed in molten chloroacetic acid (200 c.c.) maintained at 140° whilst a stream of oxygen was passed through for 50 hours. The bulk of the rubber remained undissolved, but appeared to have undergone some change since, after being extracted with acetone to remove residual chloroacetic acid, it was recovered as a tough, non-elastic, insoluble mass. The chloroacetic acid itself, decanted from the afore-mentioned insoluble matter, was very dark and yielded a brown precipitate on being poured into water. The dried precipitate (1·8 g.) (Found: Cl, 2·9%) was sparingly soluble in alcohol and in acetone, insoluble in benzene, carbon disulphide, and ethyl acetate, but readily soluble in benzene–acetone.

Attempted Oxidation in Alkaline Media.—Rubber (20 g.) was placed in 0·5*N*-alcoholic potassium hydroxide (300 c.c.) and heated at 80° whilst oxygen was passed through the solution for 40 hours. No rubber dissolved during this time, and the recovered rubber contained very little oxygen (Found: C, 87·6; H, 11·7%); this was next placed in benzene (300 c.c.) containing 100 c.c. of 0·5N-alcoholic potassium hydroxide, and the oxidation resumed at 80°. After 30 hours no extensive degree of oxidation had occurred (Found: C, 87·3; H, 11·7%). Rubber (10 g.) in pyridine (100 c.c.) was submitted to the action of oxygen at 100°. The rubber passed into solution, and after continuation of the treatment for 40 hours the pyridine was removed under reduced pressure. The residue was treated with warm aqueous hydrochloric acid (2N), taken up in ether, and this solution was well washed and dried. Removal of the ether yielded a dark brown gum {Found: C, 80·7; H, 10·7; N, trace; OH (including OH in CO_2H groups), 2·0%; CO + CHO, equivalent to 1% oxygen; equiv., 3,600; [η] (in benzene +15% methanol), 0·095, from which $M = 7{,}900$}.

Analytical Methods.—*Acidity* was determined by titration of a dilute solution of the sample (0·1 g.) in aqueous alcohol (100 c.c.) with 0·1N-sodium hydroxide, phenolphthalein being the indicator. The high dilution was necessary in order that the colour of the solution should not mask the end-point. The *acetoxyl content* of materials of small total oxygen content was determined by dissolving the sample (0·5—1·0 g.) in benzene, adding alcoholic potassium hydroxide, and refluxing the mixture for 4—6 hours in an atmosphere of nitrogen. For highly oxygenated materials, 0·1 g. was dissolved in 95% ethanol (10 c.c.), 25 c.c. of 0·2N-potassium hydroxide (aqueous) were added, and the solution was boiled for at least 4 hours in an atmosphere of nitrogen under a reflux condenser guarded by a soda-lime tube. From the alkali consumed was deducted the amount required to neutralise the acidity of the sample. The *iodine values* were determined by the Kemp–Wijs method (*Ind. Eng. Chem. Anal.*, 1934, **6**, 52): the oxidation products did not give a reaction for peroxidic oxygen and hence did not liberate iodine from potassium iodide. *Molecular weights* of the highly oxygenated materials were determined cryoscopically in benzene, and *hydroxyl contents* of materials soluble in benzene, toluene, or anisole by Bolland's method (*loc. cit.*). The highly hydroxylated products were not soluble in the foregoing solvents, and accordingly pyridine was used with a slight modification to Bolland's procedure since the Grignard pyridine complex appeared to be slightly volatile in a high vacuum. This modification involved placing a stopcock in the tube connecting the two limbs of the reaction vessel, and thereafter distilling the pyridine contained (together with a little methylmagnesium iodide) in the right-hand limb on to the sample in the other limb. Later, the stopcock was closed, and further reagent (in toluene) introduced into the right-hand limb. After the usual preliminary degassing, the stopcock was reopened, and the reagent allowed to flow on to the sample. After this point the normal procedure was followed. If there was any premature reaction with traces of the reagent which had volatilised with the pyridine, the methane so produced was confined in the closed limb of the reaction vessel and was not lost in the preliminary degassing operations.

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94. *Interchange of Hydrogen Isotopes with Complex Salts. Part I. Kinetics of the Interchange with the Luteocobaltic Complex.*

By J. S. Anderson, H. V. A. Briscoe, and N. L. Spoor.

The hydrogen of hexamminocobaltic chloride and of trisethylenediaminocobaltic chloride undergoes isotope exchange with heavy water in solutions. The interchange reaction in buffered solutions proceeds at measurable speed, according to a pseudo-unimolecular law, the reaction rate being inversely proportional to the hydrogen-ion concentration, but practically independent of the concentration of ammine, or of the proportion of deuterium that it contains. The interchange mechanism is interpreted on the basis that a metal ammine group M–NH_3 can ionise as an acid, forming a metal amide-group, M–NH_2, and hydrogen ion. There is thus a parallelism with the properties of the aquo-ammines, which form hydroxo-ammines by dissociation. There is some evidence that the ease of acid dissociation runs parallel to the stability of the ammines.

Erlenmeyer and Gartner (*Helv. Chim. Acta*, 1934, **17**, 1008) observed that the hydrogen contained in the ammonia molecules of typical cobaltammines interchanged with deuterium when the salts, *e.g.*, hexamminocobaltic nitrate, $[Co(NH_3)_6](NO_3)_3$, were dissolved in heavy water. From their approximate measurements of the extent of interchange, it appeared that all the hydrogen atoms of the ammine were involved. Bankowski (*Monatsh.*, 1935, **65**, 262), however, claimed that only one atom in diaquotetramminocobaltic chloride and three atoms in carbonatotetramminocobaltic chloride underwent interchange. This inherently improbable conclusion was criticised by Erlenmeyer, and disproved by Horiuti and Okamoto (*Sci. Papers Inst. Phys. Chem. Res. Japan*, 1937, **31**, 205), who showed, for ammines of various types, that all aquo- and ammino-hydrogen is replaceable.

Anderson, James, and Briscoe (*Nature*, 1937, **139**, 507; J., 1937, 1492) had already reached the same conclusion, and had shown further that the interchange of deuterium with complex salts in partly heavy water is slow, recording some preliminary observations on the velocity of the process. Since the typical cobaltammines are remarkably stable compounds (*e.g.*, hexamminocobaltic chloride may be warmed with concentrated hydrochloric acid for long periods without undergoing any decomposition), it is plain that the interchange of hydrogen for deuterium cannot take place by way of an initial dissociation of ammonia, followed by the equilibrium of ammonia with the heavy water. As the interchange reaction promised to be of considerable interest in relation to the general theory of the co-ordinated complex, its kinetics were investigated (during 1936—37), hexammino- and trisethylenediamino-cobaltic chlorides being used.

Experimental.

In the work of Anderson, James, and Briscoe, as in the other investigations cited, the general method of experiment had been to dissolve the cobaltammine in partly heavy water, and to observe the decrease in density of that water consequent upon the exchange of hydrogen for deuterium. For the study of reaction kinetics, this method is disadvantageous. Small changes in deuterium content, such as attend interchange reactions in dilute solutions, are most accurately and conveniently determined in solutions of low deuterium content, where the flotation method (cf. J., 1934, 1207; 1937, 1492) of determining the " heaviness " of water can be applied. In the present work, therefore, the usual procedure was reversed. Hexamminocobaltic chloride was first converted into the " heavy " salt by suitable treatment with concentrated deuterium oxide; this salt was then dissolved in normal (" light ") water, and the isotope interchange followed by observing the rate at which deuterium appeared in the solvent. The maximum final concentration of deuterium oxide encountered in the experiments was about 1·4%, corresponding to a flotation temperature of 24·01° with the float used (flotation temperature in standard water = 16·80°). This procedure had the further advantages (*a*) that the deuterium content of the solvent remained small throughout the reaction, which therefore proceeded practically to completion, and (*b*) that systems of very high deuterium content could be investigated by using relatively small amounts of heavy water.

Preparation of Materials.—Hexamminocobaltic chloride, prepared essentially by Jörgensen's method (*Z. anorg. Chem.*, 1898, **17**, 455), was rigorously purified from unchanged aquopentammine and chloropentammine: the former was converted into the latter by 3 hours' heating in a vacuum at 100°, and the chloropentammine was removed by repeated fractional precipitation with hydrochloric acid.

Trisethylenediaminocobaltic chloride was obtained by the action of ethylenediamine hydrate (30 g.) upon chloropentamminocobaltic chloride (19 g.) in water (150 c.c.) at 100°. The salt was precipitated with alcohol, and finally purified by recrystallisation, as the trihydrate, $[Co\ en_3]Cl_3,3H_2O$, from water.

Conversion of the ammines into the " heavy " salts. All manipulations involving the distillation of heavy water or the transference of samples in the course of a determination were carried out by means of vacuum apparatus of the type described previously. For the preparation of the heavy ammines, approximately 10 g. of heavy water (containing 50—100% of D_2O, according to the experiment) were distilled on to a weighed sample of the pure, thoroughly dehydrated, light salt, contained in a 50-c.c. flask attached to the apparatus by means of a standard ground joint. The salt taken did not quite saturate the solution at 60°. To facilitate interchange a small quantity of heavy ammonia was introduced into the solution by adding about 0·1 g. of calcium nitride to the heavy water just before the distillation. The flask containing the salt and heavy water was then capped and heated at 60° during 2 hours, to ensure attainment of interchange equilibrium. The heavy water was then distilled off from the salt in the vacuum apparatus, leaving the salt in the form of a hard cake. The neck of the flask was cut off, and this cake removed, and the heavy salt was finally dried in a vacuum desiccator over phosphoric oxide.

Interchange Experiments.—Preliminary measurements by Dr. F. W. James had shown that the rate of interchange was a function of the hydrogen-ion concentration of the solution. All experiments of the present series were therefore carried out in buffered solution. The choice of buffer mixture demanded consideration, in that any possibility of slow interchange of hydrogen and deuterium between the buffer and the solvent must be avoided (cf. the slow interchange reactions of acetates). Fortunately, the range of hydrogen-ion concentration covered by Sörensen's Na_2HPO_4–KH_2PO_4 buffer extended sufficiently far into the acid range for our purpose, and it seems to be free from any objection on the above grounds. The buffer solutions were prepared from M/15-solutions of the pure anhydrous salts in carbon dioxide-free distilled water, according to the usual procedure.

A suitable amount of the dry, powdered, heavy salt was weighed into a 50-c.c. flask fitted with a standard ground joint and cap. The flask was immersed in a thermostat at 20°, and 30 c.c. of the buffer solution, previously brought to the same temperature, were pipetted as rapidly as possible on to the salt. The flask was well shaken (in the thermostat), and the stop-clock started simultaneously: this addition took about 7 secs., and in no case did the time required for the salt to dissolve exceed 30 secs. The zero time of the reaction is considered to be known within ± 10 secs.

The dissolution of the salt marked the commencement of the exchange reaction, and samples (4—5 c.c.) were removed at definite intervals of time to determine the progress of the reaction: the times were so chosen as to bracket the time of half-change. A final residual sample, after standing for 24 hours, or being warmed for a short time, gave the equilibrium concentration of heavy water at $t = \infty$, from which the quantity of deuterium contained in the original salt could be calculated. Each sample withdrawn was immediately transferred to a test-tube containing a suitable excess of solid precipitant, whereby the complex cation was thrown out of solution, and the interchange sharply arrested. Anderson, James, and Briscoe used for this purpose mercuric chloride, which precipitated hexamminocobaltic mercurichloride, $[Co(NH_3)_6](HgCl_4)Cl$. In this series of experiments, it was found preferable to precipitate the hexammine salt as its sparingly soluble iodide, by running the sample of solution on to about 0·5 g. of dry powdered potassium iodide, which dissolved so quickly as to arrest the interchange almost instantaneously. As the iodide of the trisethylenediamine compound was too soluble for this device to be used, this complex was precipitated as the mercurichloride, a large excess of mercuric chloride being used. This precipitation, which required about 30 secs. for completion, was less satisfactory than that described for the hexammine, and the results are therefore less trustworthy. After precipitation, the sample was immediately filtered by means of the device shown in Fig. 1 (essentially a modified Pregl microfilter) into a flask fitted with a standard ground joint. Since no further interchange was possible, the sample could at this stage be put aside for purification.

FIG. 1.

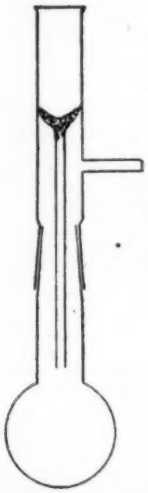
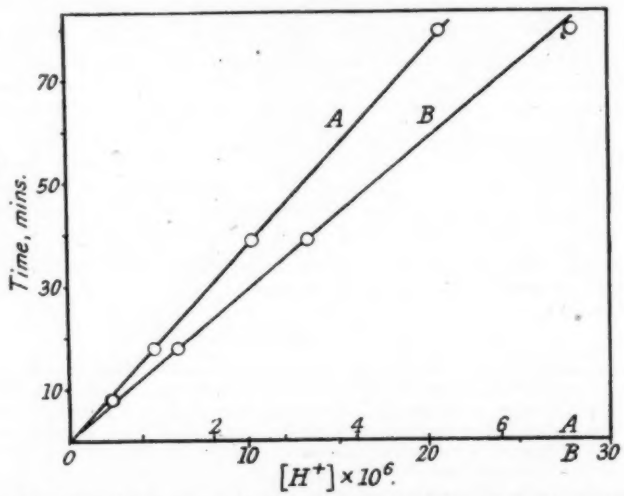


FIG. 2.



The purification of samples, and micro-flotation temperature measurements followed the lines of earlier work in these laboratories. Each sample was purified by three distillations in the vacuum apparatus described previously (J., 1937, 1492, Fig. 2). Much time was saved by distilling, at each stage, only about 90% of the water out of each specimen. With samples containing less than 1·5% of deuterium oxide—as in this work—the fractionation of isotopes resulting from this procedure is negligible when the subsequent density determinations are made only to $\pm 2\gamma d$. The original volume of filtrate was about 4 c.c.; density determinations were ultimately made on a sample of about 2·5 c.c. In the first-stage distillation (A), water was distilled from the filtrate sample (containing phosphates from the buffer mixture + excess precipitant) into a second similar 10-c.c. flask. With the trisethylenediamino-salt, to obviate the tendency of the excess of mercuric chloride to sublime over at this stage, each sample was treated with an excess of solid potassium iodide just before the distillation, thereby fixing the mecury as the non-volatile K_2HgI_4. The distillate from process (A) was boiled for 10 secs. with about 0·05 g. of sodium peroxide and 0·5 g. of potassium permanganate, cooled rapidly to 0°, and redistilled in the same apparatus. This distillate (B) was treated with about 0·05 g. of phosphoric oxide (to fix any ammonia arising from slight decomposition during the interchange reaction itself), and finally distilled into the flotation vessel (*loc. cit.*, Fig. 5). This third distillation was performed in a second vacuum apparatus reserved exclusively for this purpose. The specimen of water was poured into the flotation tube, the vessel capped with tin foil, and the flotation temperature then determined by the rapid float-velocity method already described (*loc. cit.*, p. 1497).

Results.—The interchange reaction followed a pseudo-unimolecular law, in that, for each experiment,

$$\log [HOD]_\infty/([HOD]_\infty - [HOD]_t) = kt,$$

where [HOD] is the excess concentration of heavy water in the solution at the times t and ∞. The velocity constant k is a function of $[H^+]$, and possibly also of the concentration of ammine and the "heaviness" of the ammine.

(a) *Effect of hydrogen-ion concentration.* A series of experiments was carried out with hexamminocobaltic chloride, the same concentration of the same batch of salt (0·300 g. of 53% heavy salt, in 30 c.c. of buffer solution), being dissolved in four different buffer mixtures, of original pH = 5·29, 5·59, 5·91, and 6·24 severally at 20°. The plot of the time of half-change, $t_{\frac{1}{2}}$, against the hydrogen ion activities corresponding to these values is linear. When these experiments were carried out, the authors were not cognisant of the very large effect of cobaltammine salts, with their high valency type, upon the hydrogen-ion activity of phosphate buffer mixtures. Curve *A*, Fig. 2, is plotted from the uncorrected figures, whereas curve *B* is obtained after correcting the hydrogen-ion activity of the buffers for the effect of the salt, according to the measurements of Cobb and Anderson (in the press). Neglect of the correction, although it gives incorrect numerical values for the velocity constant k, does not, in this series of measurements, invalidate the conclusions. It would appear, then, that the rate of interchange is inversely proportional to the activity of the hydrogen ion. These results are given in Table I. The velocity constants in this and the following table are the observed first-order velocity constants multiplied by $[H^+]$.

TABLE I.

Run.	Nominal pH.	True pH.	$[H^+] \times 10^6$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.	Run.	Nominal pH.	True pH.	$[H^+] \times 10^6$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.
A1	5·28	$4·54_8$	28·3	79	2·48	A3	5·89	$5·21_0$	6·2	18	2·39
A2	5·59	$4·87_1$	13·5	39	2·40	A4	6·20	$5·59_4$	2·55	8·5	2·08
											Mean 2·34

(b) *Effect of concentration of deuterium in the salt.* For this series of measurements, samples in which 88%, 60%, 16%, and 12% severally of the hydrogen was replaced by deuterium were prepared by dissolving equal weights (0·45 g.) of the 88% heavy salt in H_2O–D_2O mixtures of suitable concentration, according to the procedure used in the preparation of heavy salt (see above). The interchange experiments were then carried out in the vessel used for the preparation of each sample of salt, without transference, the same buffer solution of initial pH 5·59 being used throughout at 20°. By this technique molecularly equivalent quantities of the salt of varying molecular weight were taken, without prior knowledge of the degree of heaviness of each, which was subsequently calculated in each case from the final concentration of heavy water in the interchange experiments. The results are collected in Table II. It is clear that the rate of interchange is practically independent of the heaviness of the salt. The theoretical considerations detailed below suggest that the interchange in 12% heavy salt should take place about 1% slower than in 88% heavy salt. The precision of this series of experiments does not suffice to decide whether the rate of reaction is appreciably dependent on the deuterium content, or whether the low velocity constants found for the heavier salts (runs B1, B2) are significant. We may return to this point in a later investigation.

TABLE II.

Run.	Percentage heaviness ($= \xi$).	True pH.	$[H^+] \times 10^6$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.	Run.	Percentage heaviness ($= \xi$).	True pH.	$[H^+] \times 10^6$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.
B1	88	$4·78_0$	16·6	49	2·35	B4	30	$4·77_3$	16·9	39·5	2·97
B2	60	$4·77_7$	16·7	44	2·63	B5	16	$4·77_2$	16·9	42	2·79
B3	48	$4·77_5$	16·8	40	2·91	B6	12	$4·77_0$	17·0	42·5	2·77
											Mean 2·74

(c) *The effect of varying concentration of ammine in solution.* Before Cobb and Anderson (*loc. cit.*) had measured the effects of varying concentrations of ammines on the hydrogen-ion activities of phosphate buffer solutions, this factor constituted a very puzzling feature of the investigation. Two series of measurements were made at 20°: (C) hexamminocobaltic chloride (65% heavy) and (K) trisethylenediaminocobaltic chloride (80% heavy). In series C, the salt concentration was varied from 2·1 to 20 g./l. in a buffer solution of original pH 5·59; in series K, concentrations were varied from 6·7 to 34 g./l. in a buffer solution of original pH 5·29. Both sets of results are in Table III.

TABLE III.

Run.	Concn. of salt, g./l.	$t_{\frac{1}{2}}$, mins.	True pH.	$[H^+] \times 10^6$.	$k \times 10^7$.	Run.	Concn. of salt, g./l.	$t_{\frac{1}{2}}$, mins.	True pH.	$[H^+] \times 10^6$.	$k \times 10^7$.
C1	20·0	57	$4·70_1$	19·9	2·42	K1	34·4	66·5	$4·40_6$	39·0	4·15
C2	13·0	45	$4·80_2$	15·8	2·43	K2	26·7	58·5	$4·44_9$	36·3	4·30
C3	8·5	34	$4·90_7$	12·4	2·53	K3	17·9	44·5	$4·52_9$	29·6	4·61
C4	4·2	23·5	$5·08_4$	8·24	2·43	K4	13·4	39·5	$4·59_5$	25·4	4·45
C5	2·1	14·5	$5·26_9$	5·34	2·57	K5	6·7	27·5	$4·75_5$	17·6	4·43
				Mean	2·48					Mean	4·38

No simple relation between velocity and concentration is apparent, but when $t_{\frac{1}{2}}$ is plotted logarithmically against [ammine], a good linear relation is found, indicating apparently that: for series C, $k \propto [\text{ammine}]^{-0·56}$; for series K, $k \propto [\text{ammine}]^{-0·54}$. This peculiar dependence upon concentration at once finds its explanation in the measurements of hydrogen-ion activity (see p. 362), for this increases with the concentration of ammine according to exactly the same laws. The true pH of the solutions in each case, the actual hydrogen-ion activity, and the velocity constant calculated after correction for the variations in $[H^+]$ are recorded in cols. 4, 5, and 6 of Table III. Within the limits of error of the measurements, the velocity of interchange is independent of the concentration of ammine in the solution.

(d) *The influence of added electrolytes.* The presence of the Brönsted secondary kinetic salt effect is evident from the large effect of the complex salt on the pH of the phosphate buffer mixtures. No systematic investigation of the Brönsted primary salt effect was made, but the possibility of direct participation of ammonium and chloride ions in the reaction mechanism was eliminated by appeal to experiment. Interchange measurements were made with hexamminocobaltic chloride at 22°, 0·400 g. of 58% heavy salt in 30 c.c. of solution (original pH of buffer 5·59) being used in the presence of one molecular proportion of ammonium nitrate or of potassium chloride. The results are in Table IV.

TABLE IV.

Solution containing 13·33 g./l. of 58% heavy $[Co(NH_3)_6]Cl_3$ at 22°. True pH $4·81_0$ throughout.

Run	D1	E2	E3
Addition to solution	None	NH_4NO_3, 1 mol.	KCl, 1 mol.
$t_{\frac{1}{2}}$, mins.	29·5	30·25	29·75

(e) *The temperature coefficient of the reaction.* Measurements on both ammines were carried out at 22°, 15°, 8°, and 0°, equimolecular concentrations of the same batch of heavy salt and buffer mixtures of the same pH being used throughout each series. It has been shown by Walbum (*Biochem. Z.*, 1920, **107**, 219) and by Hastings and Sendroy (*J. Biol. Chem.*, 1924, **61**, 693) that the pH of phosphate buffer mixtures is almost independent of temperature. Hence the measurements recorded in Table V represent the true variation of reaction velocity with temperature at constant hydrogen-ion activity.

TABLE V.

Run.	Temp.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.		Run.	Temp.	$t_{\frac{1}{2}}$, mins.	$k \times 10^7$.	
D1	22°	29·5	3·64	$k_{20°}/k_{10°} = 5·4_7$ $k_{10°}/k_{0°} = 6·4_4$ $E = 28{,}400$ cals.	L1	22°	33	6·27	$k_{20°}/k_{10°} = 5·4_3$ $k_{10°}/k_{0°} = 6·4_1$ $E = 28{,}100$ cals.
D2	15	92	1·17		L2	15	102	2·03	
D3	8	322	0·333		L3	8	357	0·58	
D4	0	1400	0·0707		L4	0	1500	0·148	

DISCUSSION.

If we assume that all the hydrogen atoms in the ammine are equivalent, *i.e.*, that the partial deuteration of any one ammonia group in no way affects the probability of further interchange, we may symbolise the light hexamminocobaltic cation as $[CoN_6H_{18}]^{+++}$, and a heavy ammine cation in which x atoms of hydrogen are replaced by deuterium can be represented as undergoing interchange according to the equation

$$[CoN_6D_xH_{18-x}]^{+++} + xH_2O \longrightarrow [CoN_6H_{18}]^{+++} + xHOD$$

In dilute solutions, this reaction, as has been shown, is pseudo-unimolecular; the rate of the reaction is inversely proportional to the activity of hydrogen ions. This implies either (*a*) that hydroxyl ions participate as a reactive species in the rate-determining step, or (*b*) that the true reactive species and hydrogen ions are present in dissociative equilibrium, which is therefore shifted by changes in the hydrogen ion activity of the solution—*e.g.*, an ionic dissociation of the ammine ion, such as

$$[Co(NH_3)_5NH_3]^{+++} \rightleftharpoons [Co(NH_3)_5NH_2]^{++} + H^+$$

Such an ionisation reaction, which Garrick (*Nature*, 1937, **139**, 507) has postulated independently, is indeed essential at some stage in the interchange, in order that hydrogen may be transferred from the ammine ions to the water molecules or *vice versa*. The hexamminocobaltic cation is a co-ordinatively saturated entity, not only as far as the metal is concerned, but also with respect to the nitrogen atoms of the ammonia groups. Each of these completes its stable co-ordination number (4) by combination with the central metal atom. The actual mechanism of interchange must, however, involve at some stage the addition of hydrogen ions or water molecules to a co-ordinatively unsaturated molecule, such as is provided by the dissociation mechanism shown. As one of us has indicated elsewhere, this conception is of considerable interest in relation to the theory of co-ordination compounds, and of weak acids generally.

The heavy ammine used is, of course, a mixture of all the various possible deuterated types, *e.g.*, x (above) may have all values from 0 to 18, and the replacement of deuterium by hydrogen is brought about by a complex series of consecutive reactions. In interpreting the kinetic data, we have therefore first to establish the relation between the deuterium lost to the solution and that remaining in the salt. By a method exactly similar to that employed by Ives (J., 1938, 91) in considering the interchange of deuterium with glutaconic acid, it can easily be shown that, at equilibrium, the concentration of the deuterated ammine containing j atoms of deuterium is related to the concentration of completely light ammine by

$$c_j = \frac{\lfloor 18}{\lfloor j \lfloor 18-j} \cdot f^j[CoN_6H_{18}], \text{ where } f = \frac{k_{rH} \cdot k_{aD}}{k_{aH} \cdot k_{rD}} \frac{\{\alpha[HOD][HOH] + [HOD]^2\}}{\{[HOH]^2 + (1-\alpha)[HOD][HOH]\}}$$

In this expression, k_{aH}, k_{rH} are respectively the rates of the reactions by which hydrogen is added to or removed from the ammine; k_{aD}, k_{rD} are the similar constants relating to deuterium; α is the probability that a molecule HOD will react in such a way as to add on a deuterium atom to the ammine complex; $1-\alpha$ is the probability that HOD will so react as to add on a hydrogen atom, and [HOD] is the concentration of HOD in the solution in equilibrium with the ammine.

The total concentration of ammine in the solution $= C = \sum_{j=0}^{j=18} c_j$. As a further simplifying assumption, it will be taken that $k_{aH} = k_{aD}$, $k_{rH} = k_{rD}$, $\alpha = 1-\alpha = \frac{1}{2}$. These simplifications, which are not vital to the interpretation of the results, are justified since the partition of deuterium between ammine and water is nearly uniform. It follows from the foregoing that if we define a quantity ξ, the statistical mean heaviness of the ammine, by $\xi = \Sigma jc_j/18C$, then the isotopic composition of the material in equilibrium—*i.e.*, the initial salt and the final state—is completely defined when ξ is known.

The rate of formation of heavy water is given by the relation

$$-d[HOD]/dt = \sum_{j=0}^{j=18} j \cdot dc_j/dt$$

If the further approximation is introduced that the back reaction—regeneration of deuterated ammine by interchange with HOD—can be neglected (as is nearly true in our experiments, where the molar fraction of HOD was in all cases very small at the conclusion of the reaction), one can proceed at once to set up an approximate differential equation for the reaction. For, in this case, the ammine with j atoms of deuterium *disappears* solely by conversion into ammine with $j-1$ atoms of D, and is *formed* only by interchange from the ammine with $j+1$ atoms of D, while the probability that it will react so as to exchange D for H is given by the statistical weight j; *i.e.*,

$$dc_j/dt = -kjc_j + k(j+1)c_{j+1}$$

In this equation, the velocity constant k is a composite quantity, in which the experimentally found dependence of rate upon $[H^+]$ is implicit. Its nature will be subsequently evaluated when the particular mechanism of the reaction is considered. Then,

$$\frac{1}{k} \cdot \frac{d[HOD]}{dt} = \sum_{j=0}^{j=18} j\{jc_j - (j+1)c_{j+1}\} = + \sum_{j=0}^{j=18} jc_j$$

Hence,

$$(1/k)d[HOD]/dt = 18\xi C$$

At any time t, the concentration of HOD present in the solvent is related to the decrease in heaviness of the salt by $[HOD] = 18(\xi_0 - \xi)C$, where ξ_0, ξ, represent the statistical mean heaviness initially and at the time t respectively. Substituting for ξ in the above differential equation, we have that

$$(1/k)\mathrm{d}[HOD]/\mathrm{d}t = 18\xi_0 C - [HOD]$$

Integrating this, and setting $[HOD] = 0$ at $t = 0$, we obtain the unimolecular expression

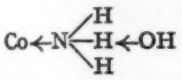
$$k = (1/t) \ln 18\xi_0 C/(18\xi_0 C - [HOD]).$$

The foregoing formal treatment of the system of consecutive reactions establishes the pseudo-unimolecular nature of the kinetics. For the explicit evaluation of k, we must consider the experimental results in relation to a particular mechanism of interchange. As was indicated above, the dependence upon hydrogen-ion activity is compatible with either of the schemes (A) or (B).

(A)
$$\begin{aligned} [CoN_6D_xH_{18-x}]^{+++} &\rightleftharpoons [CoN_6D_{x-1}H_{18-x}]^{++} + D^+ \\ [CoN_6D_{x-1}H_{18-x}]^{++} + HOH &\rightleftharpoons [CoN_6D_{x-1}H_{18-x}HOH]^{++} \\ [CoN_6D_{x-1}H_{18-x}HOH]^{++} &\longrightarrow [CoN_6D_{x-1}H_{19-x}]^{+++} + OH^- \\ D^+ + OH^- &\rightleftharpoons HOD \end{aligned}$$

(B)
$$\begin{aligned} [CoN_6D_xH_{18-x}]^{+++} + OH^- &\rightleftharpoons [CoN_6D_xH_{18-x}OH]^{++} \\ [CoN_6D_xH_{18-x}OH]^{++} &\rightleftharpoons [CoN_6D_{x-1}H_{18-x}]^{++} + HOD \\ [CoN_6D_{x-1}H_{18-x}]^{++} + H^+ &\longrightarrow [CoN_6D_{x-1}H_{19-x}]^{+++} \end{aligned}$$

These schemes are equivalent, and must lead to similar kinetic expressions. The following is based on the set of reactions (B), which readily lends itself to expansion. The transition complex may be considered as formed by the hydroxyl-bond union of hydroxide ion with ammonia hydrogen, *e.g.*, as inset, enabling the group to revert either to ammine or to amino-ion (and water) by fission at the appropriate linkage. We revert to the discussion of this idea in a later paragraph. From the partly heavy ammine, two types of complex may be formed—to be formulated as



$[CoN_6D_{x-1}H_{18-x}DOH]^{++}$, formed with statistical weight ξ,
and $[CoN_6D_xH_{17-x}HOH]^{++}$, „ „ „ „ $1 - \xi$.

We denote the concentration of the former as c_1, the rate of formation of transition complex as k_1, the rate of fission to give ammine + OH^- as k_2, and the rate of fission to give amino-ion + water as k_3. By reaction with OD^- ions from the HOD present in solution, we shall have similar complexes $[CoN_6D_{x-1}H_{18-x}DOD]^{++}$, concentration c_3, and $[CoN_6D_xH_{17-x}HOD]^{++}$, concentration c_4, formed respectively. Then

$$\begin{aligned} \mathrm{d}[HOD]/\mathrm{d}t &= k_3(c_1 + c_4 + 2c_3) + k_2(c_3 + c_4) - k_1K_w[HOD]C/[H^+] \\ * \mathrm{d}c_1/\mathrm{d}t &= \xi k_1K'_w[H_2O]c/[H^+] - (k_2 + k_3)c_1 \end{aligned}$$

Taking c_1, c_3, c_4 as stationary concentrations, we have

$$\begin{aligned} c_1 &= K'_w[H_2O]\xi Ck_1/[H^+](k_2 + k_3) \\ c_3 &= K'_w[HOD]\xi Ck_1/[H^+](k_2 + k_3) \\ c_4 &= K_w[HOD](1 - \xi)Ck_1/[H^+](k_2 + k_3) \end{aligned}$$

Hence,
$$\begin{aligned} \frac{k_2 + k_3}{k_1K_w}\frac{[H^+]}{C}\frac{\mathrm{d}[HOD]}{\mathrm{d}t} &= k_3\xi[H_2O] + k_3(1 + \xi)[HOD] + k_2[HOD] - (k_2 + k_3)[HOD] \\ &= k_3\xi([H_2O] + [HOD]) \end{aligned}$$

Making for ξ the same substitution as before, $\xi = \xi_0 - [HOD]/(18C)$, we have

$$18\frac{k_2 + k_3}{k_1k_3}\frac{[H^+]}{K_w}\frac{\mathrm{d}[HOD]}{\mathrm{d}t} = (18\xi_0 C - [HOD])([H_2O] + [HOD])$$

On integrating the above equation between the limits 0 and t, and setting $[HOD] = 0$ at $t = 0$, we obtain the final relation

$$\frac{k_1k_3}{18(k_2 + k_3)}\frac{K_w}{[H^+]} = \frac{1}{t}\frac{1}{18\xi_0 C + [H_2O]}\log_e\frac{18\xi_0 C([H_2O] + [HOD])}{[H_2O](18\xi_0 C - [HOD])}$$

This gives for the time of half-change

$$t_{\frac{1}{2}} = \frac{18(k_2 + k_3)}{k_1k_3}\frac{[H^+]}{K_w}\frac{1}{18\xi_0 C + [H_2O]}\log_e\left[2 + \frac{18\xi_0 C}{[H_2O]}\right]$$

According to this, $t_{\frac{1}{2}}$ will not be quite independent of either the concentration or the heaviness of the ammine

* We take the dissociation constant of water, $K'_w = [H^+][OH^-]/([H_2O]$ for the sake of homogeneity with the subsequent equations involving ionisation of HOD.

if the back reaction is detectable; since C is small compared with the mole-fraction of water in the system, the effect is not appreciable experimentally.

The formation of a transition complex of the type indicated appears to us a plausible hypothesis, since the reciprocal acid–base pairs (ammino-group + hydroxide ion) and (amino-ion + water) parallel exactly the state existing in solutions of aquo- or hydroxo-pentammine salts, as Garrick (*loc. cit.*) has pointed out. We venture the above rather concrete formulation of the transition state because it can be correlated with Nakatsuka's observations (*Bull. Chem. Soc. Japan*, **1936**, **11**, 629) on molecular association in these precisely analogous systems, in the presence of ammonium hydroxide: he found that, whereas addition of alkalis (sodium hydroxide or carbonate, etc.) to solutions of aquopentammine cobaltic salts caused immediate and quantitative formation of hydroxopentammine salt, yet addition of aqueous ammonia, or solutions of amines (pyridine, alkylamines, etc.) led to the formation of a new type of compound, which, although not isolable, was clearly characterised by its absorption spectrum. That the appearance of this spectrum was attended by an association of the ammine with ammonia was well attested by cryoscopic measurements. The process as interpreted by Nakatsuka can be formulated as the analogue of that which we have postulated in this discussion as leading to ionisation of the ammine, and isotope exchange:

$$\left[(NH_3)_5Co{\leftarrow}O\begin{matrix}H\\H\end{matrix}\right]^{+++} + NH_3 \rightleftharpoons \left[(NH_3)_5Co{\leftarrow}O\begin{matrix}H\\H{\leftarrow}NH_3\end{matrix}\right]^{+++} \rightleftharpoons [(NH_3)_5Co{-}OH]^{++} + NH_4^+$$

The displacement of equilibrium in the above system, and consequent quantitative formation of hydroxopentammine salt, takes place only when the solubility of the latter is sufficiently lowered by the addition of alcohol. That the association product in Nakatsuka's reaction is formed fairly quantitatively, whereas the transition complex, postulated as formed by the hexammine cation with hydroxide ions, is formed in infinitesimal concentration, is compatible with the relatively high acidity of the aquopentammine.

The foregoing kinetic analysis has been worked out for the particular case of the hexamminocobaltic cation. A general expression for the velocity constant, applicable to any ammine, would be $k_1k_3K_w/N[H^+](k_2 + k_3)$, where N is the number of interchangeable hydrogen atoms. We may proceed to compare the product $k_1k_3/(k_2 + k_3)$ for different ammines, and for ammines of different metals. In this expression, the factor $k_3/(k_2 + k_3)$ represents the probability that ionisation will follow the formation of the transition complex. Hence, k_1, the rate of formation of the transition complex, appears as the true rate-determining factor. Considering, now, the critical increments and the true velocity constants for the two salts discussed here, it is possible to make only reasonable conjectures as to the significance of the several factors. The reaction constant k_1 should not be markedly affected by substitution of a primary amine group for an ammonia molecule. On the other hand, the probability term, $k_3/(k_2 + k_3)$, is a measure of the readiness with which the co-ordinated ammino-group $Co{\leftarrow}NH_3$ passes over into the covalent amino-group $Co{-}NH_2$. The greater stability of co-ordination compounds containing ethylenediamine as against those containing ammonia may be correlated with a higher velocity constant of hydrogen isotope interchange. Constants obtained by multiplying the velocity constants found in this work by the number of interchangeable hydrogen atoms are: for $[Co(NH_3)_6]^{+++}$, $4{\cdot}54 \times 10^{-6}$; for $[Co\ en_3]^{+++}$, $5{\cdot}27 \times 10^{-6}$. We suggest that this variation from one ammine to another can be taken as reflecting principally the variation in the probability of acidic ionisation. If this be so, a new method becomes available for comparing semiquantitatively the co-ordinating powers of ammines, and the influence of the structure of the co-ordinated complex upon its stability.

To the critical increment for the interchange, the factors considered will contribute severally, and the rather high temperature coefficient is therefore comprehensible. It is noteworthy that Nakatsuka (*loc. cit.*) found that the formation of the association complex between ammonia and the aquopentammine cation is strongly dependent upon temperature. By analogy, this would indicate that the rate-determining factor k_1 in our interchange mechanism is also to be attributed a high temperature coefficient. Allowance being made for the temperature coefficient of K_w, it is clear that the factors $k_1k_3/(k_2 + k_3)$ together have a critical increment of about 14,500 cals.

The Acid Dissociation of Metal Ammines.—The conception of an acid dissociation of the ammines introduced in the foregoing discussion is not entirely novel, since for one particular class of compound—the ammines of quadrivalent platinum—the formation of aminoammines (corresponding to the hydroxoammines) had already been established by the preparative investigations of Tschugaev (*Z. anorg. Chem.*, **1924**, **137**, 1; *Compt. rend.*, **1915**, **160**, 840; **1915**, **161**, 699), and investigated further by Grünberg (*Z. anorg. Chem.*, **1924**, **138**, 333; Grünberg and Faermann, *ibid.*, **1930**, **193**, 193). These workers showed that acidopentammino- and diacidotetrammino-platinic salts, *e.g.*, $[Pt(NH_3)_5Cl]Cl_3$, $[Pt(NH_3)_4(NO_2)Cl]Cl_2$, were converted in mildly alkaline solutions into the corresponding aminoammino-salts, such as $[Pt(NH_3)_4(NH_2)Cl]Cl_2$, which as Tschugaev showed, is a base slightly weaker than aqueous ammonia. Although the corresponding amino-compound appears not to have been isolated, it is evident from pH measurements on its solutions, and from the colour change of those solutions on lowering the hydrogen-ion concentration, that $[Pt(NH_3)_6]Cl_4$ similarly furnishes an aminoammine, *viz.*, $[Pt(NH_3)_5NH_2]Cl_3$. The hexammine appears to be the strongest acid of this type; the acidity constants decrease progressively in the series $[Pt(NH_3)_6]^{4+} > [Pt(NH_3)_5Cl]^{3+} > [Pt(NH_3)_4Cl_2]^{2+}$, largely, no doubt, because of the decreasing repulsion between the hydrogen ion and the residual anion as the valency of the latter is diminished. This effect is observed in the analogous ionisation of aquo-compounds. Because of the lower positive charge of the central atom of the complex, both ammines and aquo-compounds of the tervalent metals

are inherently weaker acids than those of quadrivalent platinum. Grünberg and Faermann showed, however, that in each of the pairs of analogous acids

$$[Pt(NH_3)_5NH_3]^{4+} \text{ and } [Pt(NH_3)_5H_2O]^{4+}$$
$$[Rh(NH_3)_5NH_3]^{3+} \text{ and } [Rh(NH_3)_5H_2O]^{3+}$$

the dissociation constant of the aquo-complex is about 10^{-5} that of the ammine. On the basis of measurements by Brønsted and Volquartz on aquopentamminocobaltic chloride, the dissociation constant of $[Co(NH_3)_6]^{3+}$ should be about 10^{-11}, a value compatible with our measurements.

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95. *Interchange of Hydrogen Isotopes with Complex Salts. Part II. Kinetics of the Interchange with Platinous and Palladous Tetrammines.*

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Experiments on the interchange of hydrogen isotopes between water and complex ions have been extended to tetrammino-platinous and -palladous chlorides. The rate of interchange with ammines of different metals decreases in the order Co>Pt>Pd, and runs parallel to the stability of the complex ions. Tetrammino-palladous chloride undergoes interchange by a complex mechanism; in addition to interchange by the acid dissociation mechanism discussed in Part I (preceding paper), it reacts in acid solution by reversible dissociation of ammonia from the complex. The bearing of the results upon the general theory of complex salts is discussed.

IN Part I we deduced from the kinetics of the interchange of hydrogen between stable cobaltammines and water that the ammine complex must undergo an acid dissociation of the type $M{\leftarrow}NH_3 \rightleftharpoons M{-}NH_2^- + H^+$. If this be so, other types of ammine, and ammines of metals other than cobalt, should be worth investigation from the same viewpoint, since the kinetic velocity constants might be correlated, as we pointed out, with the stability of the ammines. We now discuss the results obtained with tetrammino-platinous and -palladous complexes, which accord in general with the ideas developed in Part I. A comparison of the palladous and platinous compounds is of particular interest in view of the gradation in ammine-forming ability in the nickel–palladium–platinum triad of metals, and the interchange experiments, as will be seen, not only afford a correlation of the "acid strength" of the complex with its general stability, but shed light also on the mechanism of breakdown of the ammines, and on the transition between the stable "luteo-complex" type and the dissociable ammoniates.

EXPERIMENTAL.

The velocity of the exchange reactions was determined by an experimental method generally similar to that described in Part I. The "heavy" ammines having been prepared, the interchange of hydrogen for deuterium was carried out in phosphate buffer solutions of suitable pH.

Tetramminoplatinous chloride was prepared by heating platinous chloride, free from platinic chloride, with aqueous ammonia at 80° for 12 hours. The solution was filtered from a little undissolved platinous chloride, and evaporated to obtain the dihydrate, $[Pt(NH_3)_4]Cl_2,2H_2O$. This was further purified by crystallisation, made "heavy" in the manner previously described, and then dehydrated in a vacuum at 100°.

Tetramminopalladous chloride monohydrate, $[Pd(NH_3)_4]Cl_2,H_2O$, was similarly obtained by the action of aqueous ammonia in excess on palladous chloride. The ammine was separated by concentration of the solution and by fractional precipitation with alcohol, and was finally recrystallised from dilute ammoniacal alcohol (Found: Pd, 40·4, 40·5. Calc.: Pd, 40·45%). The "heavy" salt was dehydrated in a vacuum over quicklime.

Potassium chloro-platinite and -palladite respectively were used as precipitants in the interchange experiments for the foregoing two salts; these precipitants, by virtue of their high solubility and rapid rate of dissolution, gave immediate quantitative precipitation of Magnus's green salt, $[Pt(NH_3)_4][PtCl_4]$, and the corresponding pink $[Pd(NH_3)_4][PdCl_4]$ respectively, and thus arrested the interchange completely. The solution was then filtered, and the water was purified before density determination, in the manner already described.

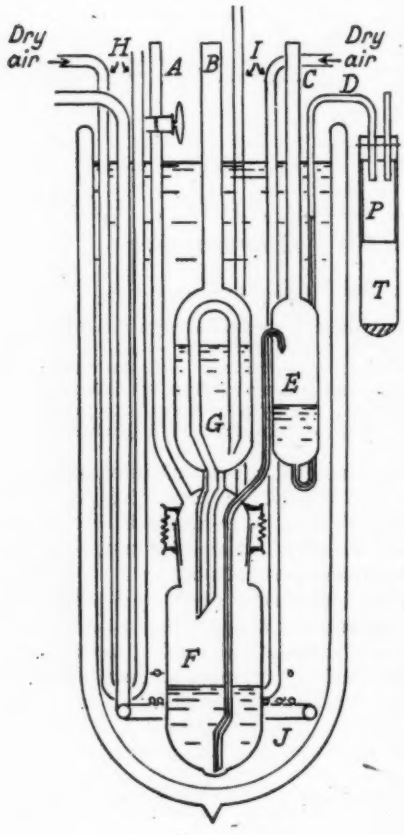
The work on tetramminoplatinous chloride comprised series of measurements on the relation of the rate of interchange to the total concentration of ammine (in which we were at that time chiefly interested) at 20° and constant hydrogen-ion activity; also on the rate of interchange in solutions of constant ammine concentration and constant pH at 0°, 7°, 14°, and 20°.

With tetramminopalladous chloride, for reasons discussed later, we made a detailed study of the influence of hydrogen-ion concentration on the rate of interchange, and extended these measurements into the regions of low hydrogen-ion activity, where the interchange reaction becomes very rapid. For this purpose, extensive series of measurements were made at 0°, and the technique was refined to permit of the study of reactions having a time of half-change of only 12 mins. at 0°. Owing to the high temperature coefficient of the reaction, it was imperative that any possibility of a change of temperature of the solution during sampling and precipitation should be avoided. The urgency of this consideration is apparent when it is borne in mind that the fastest reaction studied ($t_{\frac{1}{2}}$ = 13 mins. at 0°) would have a time of half-change of only 30 secs. at 20°. The solutions were therefore made up, sampled, and precipitated in the apparatus shown in Fig. 1, which could be immersed completely in the Dewar vessel calorimeter.

The heavy tetramminopalladous chloride was weighed into the reaction vessel F, which was attached to the rest of the apparatus by a ground joint. The apparatus was placed in a deep, cylindrical Dewar vessel, the tubes A, and B or C were stoppered, and the whole was packed around with clean crushed ice and distilled water. The buffer solution (30 c.c.), already cooled nearly to 0°, was then pipetted through B into the siphon chamber G, whereupon A or B and C

were connected to the duplicate tube systems H and I, through which dry, carbon dioxide-free, pre-cooled air could be blown into the apparatus. Attainment of thermal equilibrium was ensured by allowing the apparatus to stand for an hour, and the reaction was then started by blowing into B with the tap A open: the buffer solution then siphoned over into F, the delivery taking about 4 secs. With B closed and A open, the solution was stirred by blowing air through it by way of C and E. In order to take a sample, the automatic pipette E was filled by blowing through A. The volume of this sampling pipette was 4 c.c., but since delivery into E took place at about 1 c.c. per sec., smaller samples could be judged by blowing for the requisite time. By blowing through A and C together, the sample was discharged through the light, narrow-bore tube D into the test-tube T containing the precipitant. In order to avoid errors due to splashes upon the upper part of the test tube that was not cooled in ice, a roll of filter-paper P was fitted inside the upper two-thirds of T. This could subsequently be removed and rejected. Delivery into T occupied about 4 secs.; the test-tube was then removed from the apparatus without removing it from the ice-bath; the filter-paper P was removed, and the test-tube stoppered and vigorously shaken. Precipitation was complete within about 6 secs. after the delivery of the sample, during the whole of which time the solution was kept at 0°. During the whole of the exchange reaction, the contents of the Dewar vessel were stirred occasionally with air from the bubbler tube J; and it was shown that the temperature was constant within about 0·02°.

FIG. 1.



Results and Discussion.

(i) *Tetramminoplatinous Chloride.*—(a) *Dependence of velocity of interchange upon concentration of ammine.* Various weights of the 81% heavy salt were dissolved in 30 c.c. of phosphate buffer solution, originally made up to pH 5·91, at 20°. The results are summarised in Table I. As found with the cobaltammines, log k, when plotted against the logarithm of the concentration of ammine, approximates to a straight line; from the slope of this, k is proportional to $[\text{ammine}]^{-0\cdot21}$. As remarked in Part I, this anomalous dependence upon the concentration of the ammine at once finds its explanation when combined with our later measurements of the activity of hydrogen ions in phosphate buffer solutions, in the presence of tetramminoplatinous chloride. Over the same range of ammine concentrations, the effective $[H^+]$ varies approximately as $[\text{ammine}]^{0\cdot21}$, whilst the rate of interchange varies inversely as the activity of the hydrogen ion. From the later pH measurements, the true $[H^+]$ in each of the experiments in the series has been calculated (Col. 4, Table I), and thence the velocity constants in Col. 6. These values, and values of k in subsequent tables, are obtained by multiplying the observed first-order velocity constants by $[H^+]$. Within the limits of experimental uncertainty, the velocity of interchange is independent of the concentration of ammine.

TABLE I.

Expt.	Concn. of ammine, g./l.	$t_{\frac{1}{2}}$, mins.	True pH.	$[H^+] \times 10^6$.	$k \times 10^6$.	Expt.	Concn. of ammine, g./l.	$t_{\frac{1}{2}}$, mins.	True pH.	$[H^+] \times 10^6$.	$k \times 10^6$.
P1	48·3	35	$5\cdot54_1$	2·88	5·70	P3	12·0	26·5	$5\cdot68_2$	2·08	5·43
P2	24·0	31·5	$5\cdot61_0$	2·45	5·39	P4	6·1	22·5	$5\cdot74_7$	1·79	5·52
											Mean 5·49

(b) *The temperature coefficient of the reaction.* A standard weight (0·72 g.) of 81% heavy salt was dissolved in 30 c.c. of buffer solution, of original pH 5·91 (true pH in presence of that concentration of ammine = $5\cdot61_0$). Interchange experiments were carried out at 0°, 7°, 14°, and 20°, with the results collected in Table II. From the variation of log k with temperature, the critical increment at constant pH is calculated as 25,200 cals.

TABLE II.

Expt.	Temp.	$t_{\frac{1}{2}}$, mins.	$k \times 10^6$.	
P2	20°	31·5	5·40	$k_{20°}/k_{10°} = 4\cdot76$
Q2	14	80	2·13	$k_{10°}/k_{0°} = 5\cdot47$
Q3	7	250	0·681	$E = 25{,}200$ cals.
Q4	0	820	0·207	

(ii) *Tetramminopalladous Chloride.*—(a) *Dependence of the velocity of interchange upon the concentration of the ammine.* The velocity of interchange of 78·8% heavy tetramminopalladous chloride was measured at 0° in M/15-phosphate buffer solution of pH 7·168, $[H] = 0\cdot679 \times 10^{-7}$, complex salt concentrations varying from 0·0124 to 0·0955 g.-mol./l. being used. Under these conditions it was estimated that about 97% of the interchange proceeded *via* the true ammine type interchange (see Table V) so that the results obtained are

comparable with those for the cobalt and platinum ammines studied. Detailed results, given in Table III, show that in this case the measured first-order velocity constant of the interchange reaction is nearly independent of the initial concentration of complex salt. This was to be expected, for owing to the much higher ionic strength of the buffer mixture of pH 7·168 ($I = 0·160$) used in these experiments than that of pH 5·906 ($I = 0·080$) used with tetramminopalladous chloride, salt effects should be correspondingly less. In agreement with this, electrometric measurements showed that the change in pH of the buffer mixture on addition of the tetramminopalladous chloride used in the interchange experiments up to a concentration of 0·04M was almost negligible.

TABLE III.

Expt.	Concn., g.-mol./l.	$k_{obs.} \times 10^3$, min.$^{-1}$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^{10}$.	Expt.	Concn., g.-mol./l.	$k_{obs.} \times 10^3$, min.$^{-1}$.	$t_{\frac{1}{2}}$, mins.	$k \times 10^{10}$.
12	0·0124	14·4	48·1	9·78	15	0·0674	14·6	46·5	9·91
13	0·0243	14·1	49·0	9·57	16	0·0955	16·1	43·0	10·93
14	0·0486	13·7	50·0	9·30			Mean 14·6	47·5	9·90

(*b*) *The effect of hydrogen-ion concentration on the rate of interchange.* Table IV summarises the results of measurements made at 20°, 10°, and 0° on 0·0673M-solutions of 78·8% heavy tetramminopalladous chloride in various M/15-phosphate buffer mixtures of pH 5·288 to 7·731. Runs 1, 2, and 3 show that, in any case, the rate of interchange is not a linear function of the hydrogen-ion concentration: for a fourfold increase in hydrogen-ion concentration, from pH 5·91 to pH 5·29, the time of half-change increases by only 30%. This behaviour is in contrast with the results obtained with the cobaltammines, and the most immediate explanation would be the possibility of interchange by some mechanism peculiar to the palladous ammine. Consonant with this hypothesis was the observation that, whereas in buffer solutions of pH 6·8—7·0 tetramminopalladous chloride dissolves to give a completely colourless solution, yet in buffers of pH 5·3—5·9 the solutions are yellow. Moreover, from the most acid solution used (pH 5·29) there separated a small amount of a pale yellow, insoluble solid, which was identified as $[Pd(NH_3)_2Cl_2]$. From its colour and reaction with potassium iodide, we believe the diammine chloride prepared under these very mild conditions to be the *cis*-compound, first isolated by Grünberg and Schulman (*Compt. rend. Acad. Sci. U.R.S.S.*, 1933, **5**, 218). This, however, was not unambiguously established.

It is clear that, in the more acid solutions investigated (pH 5·3—5·9), the degradation of the tetrammine complex to the diammine chloride is incipient. Hence, deuterium may be transported from the heavy ammine to the solvent not only by the typical ammine mechanism (A), $[Pd(ND_3)_3ND_3]^{++} \rightleftharpoons [Pd(ND_3)_3ND_2]^{+} + D^{+}$, discussed in relation to the cobaltammines, but also through the direct degradative transfer of ammonia from the ammine complex to the solution. Two possible mechanisms suggest themselves, according as a chloro-ammine (B1) or an aquo-ammine (B2) is the immediate product of substitution. In either case, the formation of a triammine complex, as shown, will presumably precede the formation of diammine, this second stage being very incomplete at the hydrogen-ion concentrations under consideration.

(B1)
$$[Pd(ND_3)_4]^{++} + Cl' \longrightarrow [Pd(ND_3)_3Cl]^{+} + ND_3$$
$$ND_3 + 3H_2O \longrightarrow NH_3 + 3HOD$$
$$NH_3 + H^{+} \longrightarrow NH_4^{+}$$
$$[Pd(ND_3)_3Cl]^{+} + NH_3 \longrightarrow [Pd(ND_3)_3(NH_3)]^{++} + Cl'$$

Alternatively,

(B2)
$$[Pd(ND_3)_4]^{++} + H_2O \longrightarrow [Pd(ND_3)_3(H_2O)]^{++} + ND_3$$
$$[Pd(ND_3)_3(H_2O)]^{++} + NH_3 \longrightarrow [Pd(ND_3)_3(NH_3)]^{++} + H_2O$$
$$[Pd(ND_3)_3(H_2O)]^{++} + Cl' \longrightarrow [Pd(ND_3)_3Cl]^{+} + H_2O$$

That the degradation proceeds by the scheme (B2) appears probable when the stability and solubility of the mixed palladous ammines are taken into account. Furthermore, King (J., 1938, 1338) has shown that the platinous diammines may give rise to aquo-ammines in solution, and it has been repeatedly emphasised (*e.g.*, Drew, J., 1934, 57) that the halogen, particularly in the *cis*-diammine chloride, is more reactive in solution than would be expected.

Since, according to both schemes, (B1) and (B2), the isotope interchange depends on the dynamic equilibrium between tetrammine and triammine, which is displaced by conversion of ammonia molecules into ammonium ions, according to either scheme of reactions, the velocity of interchange of deuterium and hydrogen by this degradative mechanism would be proportional to the hydrogen-ion concentration. Hence the total rate of interchange will be given by the sum of dissociative and degradative mechanisms, *i.e.*, we may define a total velocity constant by

$$k = k_1[H^{+}] + k_2/[H^{+}].$$

This is a quadratic expression in $[H^{+}]$, and it may at once be seen by differentiation that k passes through a minimum. In terms of the reaction mechanisms, at that hydrogen-ion concentration where the two equilibria

$$[Pd(NH_3)_4]^{++} \rightleftharpoons [Pd(NH_3)_3NH_2]^{+} + H^{+}$$
$$[Pd(NH_3)_4]^{++} + H_2O \rightleftharpoons [Pd(NH_3)_3H_2O]^{++} + NH_3$$

furnish equivalent amounts of hydrogen ion and ammonia, the rate of the reaction is independent of small changes in the hydrogen-ion concentration.

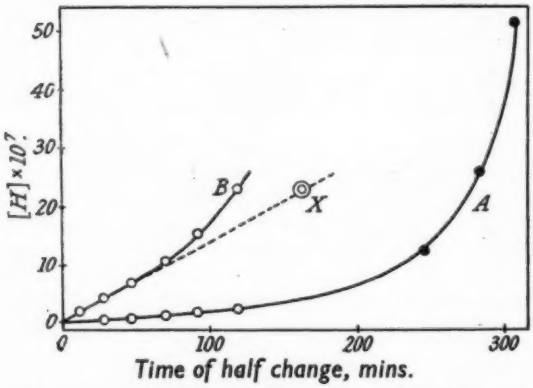
At sufficiently low hydrogen-ion concentrations, the first reaction ($\propto k_1[H^+]$) should be effectively suppressed, and interchange should occur only by the typical ammine mechanism. It was with this in mind that we extended the measurements to solutions of comparatively high pH, where a linear relation between rate of interchange and hydrogen-ion concentration might be expected. As may be seen from Fig. 2, this is borne out; up to a concentration of $[H]^+ = 0{\cdot}8 \times 10^{-7}$ the curve is linear. Above that acidity, the decomposition of the complex becomes appreciable, and the interchange occurs also by the degradative mechanism just considered.

TABLE IV.

Expt.	Temp.	pH.	$[H^+] \times 10^7$.	$k_{obs.} \times 10^3$, min.$^{-1}$.	$t_{\frac{1}{2}}$, mins.	$t_{\frac{1}{2}}$ at 0° (calc.), mins.
1	20·00°	5·288	51·5	53·9	12·9	315
2	,,	5·589	25·8	58·6	11·8	288
3	,,	5·906	12·4	67·0	10·4	254
4	10·00	5·589	25·8	12·5	55·4	—
5	0·00	6·643	2·28	5·76	120·0	—
6	,,	6·813	1·54	7·60	91·2	—
7	,,	6·979	1·05	9·81	70·7	—
8	,,	7·168	0·679	14·60	47·5	—
9	,,	7·381	0·416	23·8	29·1	—
10	,,	7·731	0·186	52·6	13·2	—

The addition of ammonium ions to a solution of pH $6{\cdot}64_3$, in which interchange by the degradative mechanism is marked, suppressed this mode of reaction, as might be anticipated. In Fig. 2 the point *X* represents the value found for the time of half-change in a solution containing 1 mol. of ammonium nitrate per mol. of ammine. The point *X* falls on the linear extrapolation of the curve through the points corresponding to expts. 8, 9, and 10, representing the velocity of interchange by the typical acid dissociation of the ammine only. The deviation of the point from the linear extrapolation ($t_{\frac{1}{2}}$, calc. = 161 mins.; obs. = 162 mins.) is within the experimental error, and is of the same order of magnitude as was found for the primary salt effect of ammonium nitrate and potassium chloride on the interchange in hexamminocobaltic chloride (Part I, p. 363).

FIG. 2.



Open circles—measurements at 0°; solid circles—calculated from measurements at 20°. For curve B, the scale of the ordinates is increased tenfold.

One of the two mechanisms of interchange can thus be satisfactorily isolated, and its velocity constant derived, from the experimental data. The similar quantitative evaluation of the second mechanism is less readily achieved, owing to the large amount of ancillary data requiring investigation. We have therefore been content to establish only the order of magnitude of the relevant velocity constant. From the value for the total velocity constant given above, it may be seen that if $[H^+]_0$ denotes the hydrogen-ion concentration at which the net velocity is a minimum (*i.e.*, $t_{\frac{1}{2}}$ is a maximum), then at $[H^+]_0$ $dk/d[H^+] = 0$, and $k_2 = k_1[H^+]_0^2$. From the measured temperature coefficient and critical increment of the total reaction (runs 2 and 4, Table III), the experimental data of runs 1, 2, and 3 may be recalculated to give the times of half-change at 0°. It is clear from the plot that the run in the most strongly acid solution (run 1) is approaching the value of $[H]^+_0$ (Fig. 2), and rough extrapolation gives $[H^+]_0$ about 50×10^{-7}, with $t_{\frac{1}{2}}$ about 300 mins. (A direct experimental repetition of run 2 at 0° was invalidated by an experimental error, which introduced an uncertainty of unknown magnitude in $t_{\frac{1}{2}}$.) Even if the above estimate of the maximum value of $t_{\frac{1}{2}}$ be in error by 10—20%, the shape of the curve remains qualitatively the same, and the value estimated for $[H^+]_0$ is not greatly altered. A second method of evaluating k_1 is to fit the experimental data of the runs 5, 6, 7, 8, 9, and 10, at the commencement of the range where the reaction becomes composite, to the expression $k = k_1[H^+] + 9{\cdot}78 \times 10^{-10}/[H^+]$. The best fit for these runs is given by $k_1 = 6{\cdot}26 \times 10^3$, and the closeness of fit with the experimental data is indicated by Table V. The values of k_1 relate to the interchange *via* the acid dissociation mechanism above and are thus comparable with constants derived from measurements on platinum and cobalt ammines.

TABLE V.

Expt.	$[H^+] \times 10^7$.	$k \times 10^3$, min.$^{-1}$, obs.	$t_{\frac{1}{2}}$, mins., obs.	$k_1 \times 10^3$, min.$^{-1}$, calc.	$k_2 \times 10^3$, min.$^{-1}$, calc.	$k \times 10^3$, min.$^{-1}$, calc.	$t_{\frac{1}{2}}$, mins., calc.
5	0·186	52·6	13·2	52·6	0·1	52·7	13·2
6	0·416	23·8	29·1	23·5	0·3	23·8	29·1
7	0·679	14·6	47·5	14·4	0·4	14·8	46·8
8	1·05	9·8	70·7	9·3	0·7	10·0	69·3
9	1·54	7·6	91·2	6·4	1·0	7·4	93·7
10	2·28	5·76	120	4·29	1·48	5·77	120

At hydrogen-ion concentrations higher than $2{\cdot}3 \times 10^{-7}$, however, the calculated curve turns over too rapidly, giving for $[H^+]_0$ about 4×10^{-7}, and for $t_{\frac{1}{2}}$, 139 mins. Inclusion of a further term in the velocity constant, to take account of the second stage in the degradation reaction (triammine ⟶ diammine) would decrease the maximum value of $t_{\frac{1}{2}}$ still further. The discrepancy between the calculated values and the results of runs 1, 2, and 3 may, however, be subject to two sources of uncertainty. In the first place, the data of runs 1, 2, and 3 were reduced to 0° by a method involving the mean temperature coefficient $k_{20°}/k_{10°}$. If the temperature coefficients and critical increments of the two concurrent reactions are very different, the time of half-change so calculated may be considerably in error. Secondly, the effect of tetramminopalladous chloride on the pH of phosphate buffer solutions, in that range of pH where decomposition is incipient, has not been fully investigated. For unavoidable reasons, the effect of the palladous ammine was investigated by us only in a buffer solution of original pH $7{\cdot}16_8$, where the change in activity of the hydrogen ions was negligible. On the other hand, the repetition at 0° of run 2, although attended with a large experimental uncertainty, indicates that at $[H^+] = 25{\cdot}8 \times 10^{-7}$, $t_{\frac{1}{2}}$ is at least 219 mins.

Much further work would be necessary to elucidate this composite interchange process. The results we have obtained suffice, however, to establish the existence in the case of tetramminopalladous chloride of two distinct processes, and to indicate the nature of the process operative in more acid solutions. We may, perhaps, designate the mechanisms of hydrogen isotope interchange as the ammine and the ammoniate types of dissociation respectively. The point of interest is that the tetramminopalladous complex can represent no special case; it is, however, unusual in that both types of reactive function are displayed under our experimental conditions. In chemical properties also, this complex stands between the metal ammoniates and the true ammines of the luteo-cobaltic type. The analogous tetramminoplatinous complex, although more stable than the palladous salt, is decomposed in fairly concentrated hydrochloric acid solution. The ammoniate type of dissociation is thus much diminished as compared with the ammine type, but its occurrence is clear. If the interchange experiments were extended to much higher hydrogen-ion concentrations, it is probable that departure from the linear relationship between hydrogen-ion concentration and rate of interchange would be found. The extremes of stability are represented by hexamminocobaltic chloride, in which the ammoniated function is completely suppressed, and the highly dissociable ammoniates of bivalent cobalt, nickel, copper, etc., in which any typical ammine functions are masked. The possession of both typical functions by such salts as tetramminopalladous chloride is strong presumptive evidence, however, that the gradation between the two extreme types of complex salt is continuous rather than—as is sometimes assumed—a question of fundamentally distinct types of chemical binding.

One may, perhaps, regard the results as having some bearing on the old problem of the relation of the metal ammines to the ammonium salts. There is, in fact, a kernel of truth in the older conception of Blomstrand and Jörgensen, that the ammines can be regarded as substituted ammonium salts. In considering the constitution of co-ordination compounds, concentration upon the rôle of the metal atom as the central atom of the complex tends to obscure the reciprocal nature of the phenomenon—*i.e.*, that the nitrogen atom of each ammonia molecule might legitimately be taken as a co-ordination centre, since it forms one co-ordinate link in virtue of the fact that it thereby acquires its stable co-ordination number, 4, and passes into the same valency state as in the ammonium ion.

A substituted ammonium ion, $[NH_3R]^+$, might be capable of dissociation by either of the mechanisms $NH_3R^+ \rightleftharpoons NH_3 + R^+$ or $NH_3R^+ \rightleftharpoons NH_2R + H^+$, the equilibrium actually set up in solution being then dependent on the relative magnitudes (i) of the electron affinities of the R^+ and H^+ ions, and (ii) of the energies of the N–H and N–R links. With alkylammonium salts (R = alkyl group), these factors operate so as to set up only one equilibrium, *viz.*, that between amine and hydrogen ion, but with metal ammines (R = metal atom, or metallic complex residue) the first of these factors is of similar order of magnitude for both reactions: the experimental evidence shows that the amino-ions are bases comparable in strength with ammonia. The second factor is sensitive to structural and other influences, as is shown by the variation in acid strength of ammines of different metals, or ammines involving other substituents (cf. ethylenediamine compounds). Moreover, herein lies the reason for the much greater acidity of oxonium compounds (such as aquopentamminocobaltic chloride) as compared with the ammonium compounds. Metal ammines may therefore dissociate, as substituted ammonium salts, in either manner, and may even—under appropriate conditions of pH, where the equilibria are shifted sufficiently—display reactions belonging to both dissociation mechanisms simultaneously. It is this state that is realised, in our experimental conditions, for the tetramminopalladous complex.

In conclusion, the experimental data for the two salts discussed in this paper are compared in Table VI, together with the relevant data for hexamminocobaltic chloride, which are included since (see Part I) the

TABLE VI.

Salt.	10^3k at 0°.	$10^3k_{0°}$.	E, cals.
$[Pd(NH_3)_4]Cl_2$	0·978*	1·17	(25,300) †
$[Pt(NH_3)_4]Cl_2$	2·07	2·48	25,200
$[Co(NH_3)_6]Cl_3$	7·67	13·8	28,400

$k = k_{obs.} \times [H^+]$; $k_{0°} = k \times$ number of exchangeable hydrogen atoms.

* Velocity constant for true ammine-type interchange only.
† Overall value for both mechanisms of interchange.

values of k multiplied by the number of interchangeable hydrogen atoms should be comparable even for ammines of different types. Two effects may be discerned in the above data. First, it is clear that, as we have supposed, the velocity constant of hydrogen interchange does run parallel with the stability of complex ammines; and secondly, an increase in the valency of the central atom of the complex is accompanied by a very definite increase in the acid strength of the complex-bound ammonia, as was postulated by Grünberg and Faermann (*Z. anorg. Chem.*, 1930, **193**, 230); the existence of such an effect was predicted by Kossel in his original application of electronic ideas to the problem of valency (*Ann. Physik*, 1916, **49**, 323).

We are glad to record our indebtedness to the Mond Nickel Co. Ltd., for the generous loan of the precious metal used in this investigation.

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96. *Derivatives of* 1 : 2 : 4 : 5-*Tetrachlorobenzene. Part II.* N-*Nitroamino-compounds.*

By A. T. PETERS, F. M. ROWE, and D. M. STEAD.

Nitration of 2 : 3 : 5 : 6-tetrachloroacetanilide gave solely 2 : 3 : 5 : 6-*tetrachloro*-N-*nitroacetanilide* (I), hydrolysed to 2 : 3 : 5 : 6-*tetrachloro*-N-*nitroaniline* (II), whereas nitration of 2 : 3 : 5 : 6-tetrachloroaniline gave (II) and 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline. Excess of nitric acid converts 2 : 3 : 5 : 6-tetrachloroaniline or (II) into 2 : 3 : 5 : 6-*tetrachloro*-4-*nitro*-N-*nitroaniline* (III). Reactions of (I), (II), and (III), involving elimination or replacement of the substituted amino-group, are described. Both (II) and (III) form N-*methyl* derivatives with alkaline methyl sulphate.

IN attempts to prepare 2 : 3 : 5 : 6-tetrachloro-4-nitroacetanilide by nitrating 2 : 3 : 5 : 6-tetrachloroacetanilide, the sole nitration product melted with vigorous evolution of oxides of nitrogen, and was partly decomposed in boiling alcohol or benzene, but crystallisation from ligroin gave 2 : 3 : 5 : 6-*tetrachloro*-N-*nitroacetanilide* (I) quantitatively. On boiling with xylene, (I) was converted into 2 : 3 : 5 : 6-tetrachloroacetanilide, 1 : 2 : 4 : 5-tetrachlorobenzene, and a little chloranil, whilst boiling toluene afforded the last two substances and some pentachlorobenzene. The *N*-nitroacetamido-group in (I) was replaced by chlorine or bromine, and halogen also introduced in position 4, by heating with hydrochloric or hydrobromic acid in acetic acid and gave hexachlorobenzene or 2 : 3 : 5 : 6-tetrachloro-1 : 4-dibromobenzene, respectively, but heating (I) with hydriodic acid in acetic acid gave 2 : 3 : 5 : 6-tetrachloroaniline. Orton (J., 1902, **81**, 501) found no evidence of *N*-nitration by the action of nitric acid on *s*-trihalogenoacetanilides. Hydrolysis of (I) with aqueous sodium hydroxide or alcoholic hydrochloric acid gave 2 : 3 : 5 : 6-*tetrachloro*-N-*nitroaniline* (II), which was also obtained, together with 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline, by nitrating 2 : 3 : 5 : 6-tetrachloroaniline. Attempted acetylation of (II) by acetyl chloride resulted in the formation of a mixture of penta- and hexa-chlorobenzene, probably due to formation and decomposition of (I). On the other hand, Macciotta (*Gazzetta*, 1930, **60**, 408) prepared 2 : 3 : 4 : 6-tetranitro-*N*-nitroacetanilide by the action of acetyl chloride on 2 : 3 : 4 : 6-tetranitro-*N*-nitroaniline. The nitro-group in (II) migrates on boiling with acetic acid and 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline is formed to a small extent.

Nitration of 2 : 3 : 5 : 6-tetrachloroaniline with excess of nitric acid gave 2 : 3 : 5 : 6-*tetrachloro*-4-*nitro*-N-*nitroaniline* (III), which was also obtained less readily from 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline.

Both (II) and (III) were decomposed by hydrochloric or hydrobromic acid in acetic acid to give hexachlorobenzene or 2 : 3 : 5 : 6-tetrachloro-1 : 4-dibromobenzene, respectively, and nitrous acid converted both (II) and (III) into diazonium salts to a slight extent as was demonstrated qualitatively by coupling and isolating derived azo-dyes. Methylating (II) and (III) with alkaline methyl sulphate gave 2 : 3 : 5 : 6-*tetrachloro*-N-*nitromethylaniline* and its 4-*nitro*-derivative, respectively.

EXPERIMENTAL.

Microanalyses were carried out by Dr. G. Weiler and Dr. F. B. Strauss, of Oxford.

2 : 3 : 5 : 6-*Tetrachloro*-N-*nitroacetanilide* (I).—2 : 3 : 5 : 6-Tetrachloroacetanilide (10 g.), acetic anhydride (60 c.c.), and nitric acid (d 1·5; 4 c.c.) were gradually warmed to 50°, and the mixture poured on ice. The N-*nitro*-compound crystallised from ligroin in small, brittle, fawn needles, m. p. 131° (vigorous decomp. with evolution of oxides of nitrogen) (yield, 11·6 g.; 100%) (Found: C, 30·7; H, 1·45; N, 9·0; Cl, 44·6. $C_8H_4O_2N_2Cl_4$ requires C, 30·2; H, 1·3; N, 8·8; Cl, 44·65%).

Reactions of 2 : 3 : 5 : 6-*Tetrachloro*-N-*nitroacetanilide.*—(*a*) 2 : 3 : 5 : 6-Tetrachloro-*N*-nitroacetanilide (6·4 g.) was refluxed with toluene (10 c.c.) for 20 minutes; a vigorous reaction was accompanied by evolution of oxides of nitrogen. On distilling with steam, the toluene was followed by an aqueous distillate containing a yellow solid; extraction of the total aqueous and solid distillate with ether, removal of the ether, and fractional crystallisation of the residue from alcohol gave 1 : 2 : 4 : 5-tetrachlorobenzene, m. p. and mixed m. p. 137—139°, pentachlorobenzene, m. p. and mixed m. p. 84°, and a little chloranil. When xylene was used in place of toluene, 2 : 3 : 5 : 6-tetrachloroacetanilide (0·4 g.), m. p. and mixed m. p. 213—214°, was obtained in addition to 1 : 2 : 4 : 5-tetrachlorobenzene and chloranil.

(*b*) Compound (I) (5 g.), acetic acid (130 c.c.), and hydrochloric acid (50 c.c.) were refluxed for 1 hour. The crystals which separated were recrystallised from acetic acid, forming colourless needles, m. p. and mixed m. p. with hexachlorobenzene, 226—227° (with sublimation) (Found: Cl, 74·7. Calc. for C_6Cl_6: Cl, 74·7%).

(*c*) Compound (I) (2 g.), acetic acid (50 c.c.), and 60% hydrobromic acid (10 c.c.) were refluxed for 15 minutes and

cooled; 2 : 3 : 5 : 6-tetrachloro-1 : 4-dibromobenzene crystallised from acetic acid in fine colourless needles, m. p. 246—247° (with sublimation) (yield, 1·2 g.; 51%), identical with that obtained by brominating 1 : 2 : 4 : 5-tetrachlorobenzene (cf. Mouneyrat and Pouret, *Compt. rend.*, 1899, **129**, 605).

(*d*) Compound (I) (2 g.), acetic acid (50 c.c.), and hydriodic acid (*d* 1·7; 10 c.c.) were refluxed for 45 minutes, and the mixture diluted with water. 2 : 3 : 5 : 6-Tetrachloroaniline crystallised from alcohol in cream-coloured needles, m. p. and mixed m. p. 107—108°.

2 : 3 : 5 : 6-*Tetrachloro*-N-*nitroaniline* (II).—(*a*) 2 : 3 : 5 : 6-Tetrachloro-*N*-nitroacetanilide (4 g.) was refluxed with 3% aqueous sodium hydroxide (100 c.c.) for 5 minutes, and the mixture filtered hot (charcoal). On cooling, colourless leaflets of a sodium salt separated, which decomposed vigorously at *ca.* 290°; the mixture was acidified with hydrochloric acid, and the precipitate of 2 : 3 : 5 : 6-*tetrachloro*-N-*nitroaniline* crystallised from aqueous alcohol, forming colourless prisms or leaflets, m. p. 145—146° (vigorous decomp.) (yield, 3 g.; 86·7%) (Found: C, 26·3; H, 1·0; N, 10·35; Cl, 51·7. $C_6H_2O_2N_2Cl_4$ requires C, 26·1; H, 0·7; N, 10·1; Cl, 51·45%). Hydrolysis was also effected with alcoholic hydrochloric acid (yield, 75%).

(*b*) A mixture of 2 : 3 : 5 : 6-tetrachloroaniline (10 g.), nitric acid (*d* 1·5; 20 c.c.), and acetic acid (50 c.c.) was slowly heated to 60°, kept at this temperature for 5 minutes, and poured on ice. Extraction of the precipitate with hot dilute sodium carbonate solution gave an insoluble residue of 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline (yield, 3·6 g.; 31·6%) and an extract which on acidification with acetic acid afforded 2 : 3 : 5 : 6-tetrachloro-*N*-nitroaniline, m. p. and mixed m. p. with the product from (*a*), 145—146° (decomp.) (yield, 6·9 g.; 57·8%).

Reactions of 2 : 3 : 5 : 6-*Tetrachloro*-N-*nitroaniline*.—(*a*) Compound (II) (5·5 g.) was refluxed with acetyl chloride (20 c.c.) for 30 minutes, the excess of acetyl chloride removed under reduced pressure, and the residue dissolved in alcohol and added to water; the product (4·7 g.) was fractionally crystallised from alcohol, giving colourless needles, m. p. 226—227° (with sublimation), of hexachlorobenzene, and more soluble colourless needles, m. p. 84—85°, of pentachlorobenzene.

(*b*) Compound (II) (1·5 g.) was boiled with acetic acid (3 c.c.) for 2 minutes; 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline, m. p. and mixed m. p. 216° (yield, 0·15 g.; 10%), separated.

(*c*) Compound (II) (1·4 g.) in acetic acid (20 c.c.) was refluxed with hydrochloric acid (5 c.c.) or 60% hydrobromic acid (5 c.c.) for 20 minutes, and gave hexachlorobenzene, m. p. 226—227° (yield, 0·6 g.; 41%), or 2 : 3 : 5 : 6-tetrachloro-1 : 4-dibromobenzene, m. p. 246—247° (yield, 1·3 g.; 68·4%), respectively.

2 : 3 : 5 : 6-*Tetrachloro*-4-*nitro*-N-*nitroaniline* (III).—2 : 3 : 5 : 6-Tetrachloroaniline (3 g.) was added to acetic acid (15 c.c.) and nitric acid (*d* 1·5; 10 c.c.), and the mixture gradually warmed to 50°, kept at this temperature for 3 minutes, and poured on ice. The precipitate was extracted with hot aqueous sodium carbonate, the extract acidified with hydrochloric acid, the precipitate dissolved in ether, and excess of ligroin added, whereupon 2 : 3 : 5 : 6-*tetrachloro*-4-*nitro*-N-*nitroaniline* crystallised in small brownish needles, m. p. 88—95° according to the rate of heating (yield, 3·9 g.; 93·3%) (Found: C, 23·3; H, 0·8; N, 12·9; Cl, 44·4. $C_6HO_4N_3Cl_4$ requires C, 22·4; H, 0·3; N, 13·1; Cl, 44·2%), which were rapidly turned yellow by light or heat. It was also obtained when 2 : 3 : 5 : 6-tetrachloro-4-nitroaniline (5·5 g.) was added to nitric acid (*d* 1·5; 20 c.c.) at 0°, and the mixture poured on ice.

On refluxing compound (III) (1 g.) in acetic acid (20 c.c.) with addition of hydrochloric acid (5 c.c.) or 60% hydrobromic acid (5 c.c.) for 10 minutes, hexachlorobenzene or 2 : 3 : 5 : 6-tetrachloro-1 : 4-dibromobenzene, respectively, was obtained.

Action of Nitrous Acid on Compounds (II) *and* (III).—2 : 3 : 5 : 6-Tetrachloro-*N*-nitroaniline (0·28 g.) or its 4-nitro-derivative (0·32 g.), sodium nitrite (0·07 g.), and 2-hydroxy-3-naphthanilide (0·13 g.) were dissolved in a hot solution of sodium hydroxide (0·4 g.) in water (200 c.c.) and added to boiling 70% aqueous acetic acid (200 c.c.); the corresponding azo-compounds were formed in small amounts. 2 : 3 : 5 : 6-Tetrachlorobenzeneazo-2′-hydroxy-3′-naphthanilide crystallised from acetic acid in red needles, m. p. and mixed m. p. with a specimen prepared from 2 : 3 : 5 : 6-tetrachloroaniline 260° (decomp.), and its 4-nitro-derivative separated from amyl alcohol in deep red needles, m. p. and mixed m. p. 296° (decomp.) (cf. this vol., p. 234).

2 : 3 : 5 : 6-*Tetrachloro*-N-*nitromethylaniline*.—Methyl sulphate (3·3 c.c.) and 10% aqueous sodium hydroxide (10 c.c.) were added gradually to 2 : 3 : 5 : 6-tetrachloro-*N*-nitroaniline (2·8 g.) in 5% aqueous sodium hydroxide (10 c.c.), the mixture raised slowly to the b. p., boiled for 2 minutes, and cooled, and the product extracted with ether. 2 : 3 : 5 : 6-*Tetrachloro*-N-*nitromethylaniline* crystallised from alcohol in colourless, lustrous plates, m. p. 138—139° (yield, 1·9 g.; 65·5%) (Found: C, 29·2; H, 1·7; N, 9·8; Cl, 48·9. $C_7H_4O_2N_2Cl_4$ requires C, 29·0; H, 1·4; N, 9·65; Cl, 48·9%).

2 : 3 : 5 : 6-*Tetrachloro*-4-*nitro*-N-*nitromethylaniline*.—2 : 3 : 5 : 6-Tetrachloro-4-nitro-*N*-nitroaniline (3·2 g.) in 4% aqueous sodium hydroxide (25 c.c.) with methyl sulphate (4·5 c.c.) at 50° for 20 minutes gave the N-*methyl* derivative, which separated from alcohol in fine, almost colourless needles, becoming yellow at 110°, and melting at 171—175° (decomp.) (yield, 1 g.; 30%) (Found: C, 26·0; H, 1·2; N, 13·0; Cl, 41·6. $C_7H_3O_4N_3Cl_4$ requires C, 25·1; H, 0·9; N, 12·5; Cl, 42·4%).

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97. *Hydroxyalkylamino-Acids. Part I.*

By WESLEY COCKER.

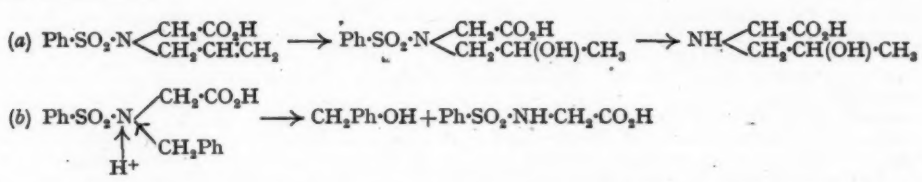
Hydrolysis of arylsulphonyl derivatives of *N*-allylglycine, *N*-allylalanine, and *N*-β-methylallylglycine with boiling 60% sulphuric acid gave N-*β-hydroxypropylglycine*, a syrup, and a quantitative yield of glycine and *iso*butaldehyde respectively.

N-*β-Hydroxyisobutylglycine* was obtained by hydrolysis of *mesitylenesulphonyl-β-methylallylglycine*, and N-*β-hydroxypropylalanine* by condensation of β-hydroxypropylamine with ethyl α-bromopropionate.

When treated with cold concentrated sulphuric acid, N-*benzenesulphonyl*-N-*allylglycine* gave N-*benzenesulphonyl*-6-*methyl*-2-*morpholone*, its p-*toluenesulphonyl* analogue gave N-p-*toluenesulphonyl*-N-*β-hydroxypropylglycine*, and N-*benzene*- and N-p-*toluene-sulphonyl-β-methylallylglycines* gave the corresponding derivatives of 6 : 6-dimethyl-2-morpholone.

Bromination of the arylsulphonyl derivatives of *N*-allylglycine and their esters gave dibromides, decomposable by sodium hydroxide into arylsulphonylglycine and acraldehyde. Attempts to effect ring closure of the dibromides to yield *N*-arylsulphonyl-4-bromoproline were ineffective.

Previous investigation (Cocker, J., 1937, 1693) showed that debenzylation takes place when *N*-benzenesulphonyl-*N*-benzylglycine is treated with boiling 60% sulphuric acid. It has now been shown that, despite the similar directive effects of the allyl and the benzyl group, the main product of the similar treatment of N-*benzenesulphonyl*-N-*allylglycine* is dl-N-β-*hydroxypropylglycine* owing to hydration in the three-carbon chain; the odour of propaldehyde and acetone perceptible during the hydrolysis, however, indicates partial three-carbon chain elimination:



Hydration in (*a*) takes place prior to the removal of the arylsulphonyl group, since *N*-allylglycine remains unchanged after prolonged boiling with 60% sulphuric acid.

N-Benzenesulphonyl-*N*-allylglycine, when treated with cold concentrated sulphuric acid, is converted into N-*benzenesulphonyl*-6-*methyl*-2-*morpholone* (the lactone of *N*-benzenesulphonyl-*N*-β-hydroxypropylglycine), but the p-*toluenesulphonyl* analogue gives the corresponding *hydroxy-acid*; both products yield *N*-β-hydroxypropylglycine with boiling 60% sulphuric acid. The *benzene*- and the p-*toluene*-*sulphonyl* derivative of β-methylallylglycine yield the corresponding derivatives of 6 : 6-dimethyl-2-morpholone, which are formed as soon as a solution of the sodium salt of the corresponding hydroxy-acid is acidified. Conversely, the unsubstituted morpholones are hydrolysed even by boiling water (Knorr, *Annalen*, 1899, **307**, 203).

The increased stability of the substituted morpholones is due to the electron-attracting arylsulphonyl group, which effect is greater in the benzenesulphonyl group than in the *p*-toluenesulphonyl group.

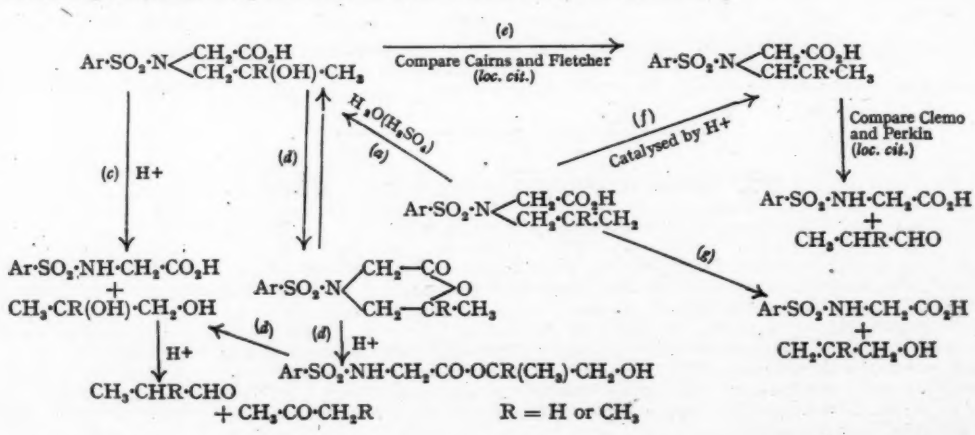
The hydration of allyl compounds has been observed by many workers (for references, see Burgin, Hearne, and Rust, *Ind. Eng. Chem.*, 1941, **33**, 385; Brachfelt and Smola, Austrian Pat. 135,351, 1935). In all cases secondary alcohols are produced.

In spite of the electron-attractive properties of the arylsulphonyl group the proton attached itself to the γ-carbon atom in all the hydrations performed. This was proved by oxidation of the hydration product of benzenesulphonylallylglycine with sodium hypoiodite, iodoform being obtained, and by the synthesis, by condensation of β-hydroxypropylamine with ethyl bromoacetate, of *N*-β-hydroxypropylglycine, the arylsulphonyl derivatives of which were identical with the hydration products of the corresponding arylsulphonylallylglycines. The constitution of the hydration product of the arylsulphonyl-β-methylallylglycines was similarly proved.

Attempts to add the elements of hydrogen chloride or bromide to the arylsulphonylallylglycines were unsuccessful; indeed, these compounds could be esterified with saturated alcoholic hydrogen chloride, but esterification of the arylsulphonyl-β-methylallylglycines under similar conditions yielded ethyl *N*-arylsulphonyl-*N*-β-chloro*iso*butylaminoacetates.

Unlike the arylsulphonylallylglycines, the corresponding β-methylallylglycines gave theoretical quantities of glycine on treatment with boiling 60% sulphuric acid, the side chain being removed as *iso*butaldehyde. Only a small proportion of the allylglycines suffered side-chain elimination and then as a mixture of acetone and propaldehyde.

The following reactions are possible in this three-carbon chain elimination.



Reaction (*c*) involves the attack of the proton at the tertiary nitrogen atom assisted by the electron-donating side chain. In view of the small difference in electron-releasing effect of the β-hydroxypropyl and the propyl

group on the one hand and the β-hydroxy*iso*butyl and the *iso*butyl group on the other and the fact that the propyl and the *iso*butyl group are not eliminated in similar circumstances (compare Cocker and Harris, J., 1940, 1290), such a mechanism is not likely to lead to elimination of the three-carbon chain. Reaction (*d*) is similar to (*c*). Both reactions lead to aldehydic or ketonic products or both. When R = H, the glycol is methylethyleneglycol, which yields a mixture of acetone and propaldehyde on pinacolinic change; but when R = CH_3, only *iso*butaldehyde is formed (compare Nevrole, *Ber.*, 1876, **9**, 448; Eltekow, *Ber.*, 1878, **11**, 990).

Cairns and Fletcher (*J. Amer. Chem. Soc.*, 1941, **63**, 1034) showed that β-hydroxypropylarylbenzenesulphonamides readily give propaldehyde on treatment with acid according to the reaction

$$Ar\cdot SO_2\cdot NH\cdot CH_2\cdot \underset{\displaystyle OH}{\underset{\displaystyle \downarrow}{\underset{\displaystyle H^+}{CH}}}\cdot CH_3 \longrightarrow Ar\cdot SO_2\cdot NH\cdot CH{:}CH\cdot CH_3 + H^+$$

$$\longrightarrow Ar\cdot SO_2\cdot N{:}CH\cdot CH_2\cdot CH_3 \longrightarrow Ar\cdot SO_2\cdot NH_2 + CH_2\cdot CH_2\cdot CHO$$

This suggests that when R = H, lactonisation as in (*d*) prevents the operation of reaction (*e*), which would lead to complete elimination of the three-carbon chain. Instead the removal of the arylsulphonyl group from the lactone proceeds normally, yielding the unstable free morpholone, which gives the hydroxy-acid. Traces of acetone and propaldehyde formed probably arise as shown in reaction (*d*).

None of the other reactions apply when R = H, as they lead to the production of only one carbonyl compound. Also unsubstituted allyl compounds undergo negligible tautomerism (compare Burgin, Hearne, and Rust, *loc. cit.*), which rules out reaction (*f*), and lactonisation is probably much more rapid than dehydration as in (*e*).

When R = CH_3, if the unsaturated acid is the starting material, reaction (*e*) or (*f*) is possible, although (*f*) is more likely, as conversion of β-methylallyl compounds into dimethylvinyl compounds is rapid and almost complete in the presence of hot sulphuric acid (compare Burgin and co-workers, *loc. cit.*). If the lactone is the starting material, it is possible that it reverts to the hydroxy-acid and then by reaction (*e*) to the dimethylvinyl compound.

The last stage of the mechanism of Cairns and Fletcher is not applicable, as we are dealing with a tertiary nitrogen atom, but it is unnecessary, since Clemo and Perkin (J., 1924, **125**, 1805) showed that vinyl derivatives of tertiary nitrogen compounds are readily decomposed under acid conditions, yielding aldehydes. This applies in compounds now under discussion.

Reaction (*g*) is also a possibility, but whereas β-methylallyl alcohol, produced when R = CH_3, is known to yield *iso*butaldehyde on treatment with acid, allyl alcohol, produced when R = H, is unaffected or yields acraldehyde.

No tautomerism takes place previous to treatment with acid, since it has been shown by ozonolysis that the arylsulphonyl-allyl- and -β-methylallyl-glycines are true allyl compounds. In every case the volatile compound from the decomposition of the ozonides was formaldehyde, and whilst the expected aldehyde from the other part of the ozonide of the former sulphonyl compound was not obtained crystalline, its 2 : 4-dinitrophenylhydrazone was isolated. The ketone from benzenesulphonyl-β-methylallylglycine was obtained in crystalline condition.

In view of the easy removal of the β-methylallyl group with sulphuric acid the hydrolysis of *N-mesitylenesulphonyl-N-β-methylallylglycine* was performed, a boiling mixture of glacial acetic and concentrated hydrochloric acids being used (compare Cocker, J., 1937, 1695). *β-Hydroxyisobutylglycine* was thus obtained. The reaction probably involves the addition of hydrogen chloride to the methylallyl group, followed by the removal of the mesitylenesulphonyl group and substitution of OH for Cl in the treatment with silver oxide to remove the excess of hydrochloric acid.

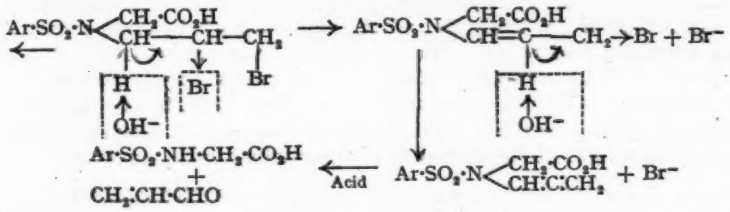
The arylsulphonylallylglycines readily give dibromides of the type $Ar\cdot SO_2\cdot N(CH_2\cdot CO_2H)\cdot CH_2\cdot CHBr\cdot CH_2Br$. These lose bromine and become unsaturated on boiling with zinc and acetic acid, are reduced by Raney nickel and hydrogen at slightly above atmospheric pressure with the production of arylsulphonylpropylglycines, and are decomposed by hot dilute aqueous sodium hydroxide to give a solution containing bromidion which on acidification even at 0° yields a mixture of acraldehyde, arylsulphonylglycine, and a small quantity of a monobromo-compound.

The monobromo-compound from *p*-toluenesulphonylallylglycine is unsaturated, and is immediately decomposed by hot dilute mineral acid with the production of a mixture of acraldehyde and a substance with the odour of propaldehyde, most likely β-bromopropaldehyde. This reaction with acid suggests that the monobromo-compound is a vinyl compound (compare Clemo and Perkin, *loc. cit.*) and throws light on the mechanism of the decomposition of the dibromide. Only very small quantities of the monobromo-compound could be obtained, but ozonolysis experiments in sodium bicarbonate solution gave a volatile aldehyde from which a 2 : 4-dinitrophenylhydrazone containing no bromide was obtained. The bromine was no doubt removed by hydrolysis during the steam distillation of the alkaline solution.

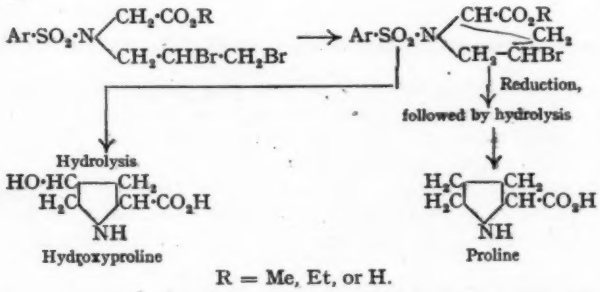
Analysis and m. p. of the 2 : 4-dinitrophenylhydrazone corresponded to that of glycollaldehyde 2 : 4-dinitrophenylhydrazone. The monobromo-compound is therefore probably

$C_6H_4Me\cdot SO_2\cdot N(CH_2\cdot CO_2H)\cdot CH{:}CH\cdot CH_2Br$

and the mechanism of the decomposition of the dibromide now suggested is:



Since the dibromides were obtained in good yield, their possible ring closure was investigated with a view to the following transformations:



R = Me, Et, or H.

However, all attempts to cyclise the methyl or the ethyl esters or the free acids led either to the recovery of the starting material or to gums. The following condensing agents were used: silver oxide, sodium in boiling xylene, copper bronze in boiling nitrobenzene.

Attempts were also made to brominate the acetate chain so as to assist ring closure. α-Bromination was never successful and it seems that the α-hydrogen atom is firmly bound by a still basic nitrogen atom. The introduction of the *m*-nitrobenzenesulphonyl group did not influence the reactivity towards bromine.

Further work is proceeding with a view to obtain the γ-bromopropyl derivative of the arylsulphonylglycines, to which more vigorous methods of ring closure can be applied.

Experimental.

Benzene- and *p*-toluene-sulphonyl derivatives of the various amino-acids are described. The former are preferable in view of their greater readiness to crystallise, but at times benzenesulphonyl chloride was not available.

N-*Benzenesulphonyl*-N-*allylglycine* (I).—A mixture of benzenesulphonylglycine (3 g.) in 3N-sodium hydroxide (15 c.c.) and allyl bromide (3 g.) was refluxed for 3 hours on the water-bath, cooled to 0°, filtered, and acidified with concentrated hydrochloric acid, and the precipitate washed, dried, and crystallised from benzene, forming long colourless prisms (2·0 g.), m. p. 107° (Found: C, 51·8; H, 5·1; N, 5·6. $C_{11}H_{13}O_4NS$ requires C, 51·8; H, 5·1; N, 5·5%).

N-p-*Toluenesulphonyl*-N-*allylglycine* (II), prepared in the same way, formed long thin prisms, m. p. 109—110° (Found: C, 53·7; H, 5·9. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%).

The identity of the above compounds was confirmed as follows: (i) Both rapidly decolourised bromine water and alkaline permanganate. (ii) Compound (II) (1·5 g.), dissolved in chloroform (20 c.c.), was subjected to a stream of 8% ozonised oxygen for 5½ hours. The chloroform was then removed in a vacuum at 20°, the syrupy residue steam-distilled, and formaldehyde identified by the dimedon derivative, m. p. and mixed m. p. 191—192°. The residue from the steam-distillation was extracted several times with ether, from which an oil was obtained the 2:4-*dinitrophenylhydrazone* of which crystallised from dilute alcohol in orange micro-prisms, m. p. 173—174° (Found: C, 45·4; H, 3·4. $C_{17}H_{17}O_8N_5S$ requires C, 45·2; H, 3·8%). This agrees with the 2:4-dinitrophenylhydrazone of *N*-*p*-toluenesulphonyl-*N*-aldehydomethylglycine.

Ethyl *N*-benzenesulphonyl-*N*-allylaminoacetate (III), prepared by allylation of ethyl benzenesulphonamidoacetate with allyl chloride in sodium ethoxide solution or by esterification of (I), was a colourless oil, b. p. 172—173°/1 mm. Hydrolysis with dilute sodium hydroxide solution yielded (I).

dl-N-*β-Hydroxypropylglycine* (IV).—Compound (I) (9 g.) was refluxed (125°) with 60% sulphuric acid (9·4 c.c. of concentrated acid, 11·7 c.c. of water) for 4½ hours, and the mixture then treated according to Cocker and Lapworth (J., 1931, 1894). The required *amino-acid* crystallised from methyl alcohol in colourless rectangular prisms (2 g.), m. p. 194—195° (decomp.) (Found: C, 45·2; H, 8·0; N, 10·4. $C_5H_{11}O_3N$ requires C, 45·1; H, 8·3; N, 10·5%). The acid had a sweet taste, was readily soluble in water but only sparingly in boiling alcohol, was non-hygroscopic, and gave the usual deep coloration with copper acetate.

N-*Benzenesulphonyl*-6-*methyl*-2-*morpholone* (V).—Treatment of (IV) in alkaline solution with benzenesulphonyl chloride and acidification of the solution gave (V). It crystallised from dilute alcohol in colourless plates, m. p. 128—128·5°, which dissolved slowly in sodium hydroxide solution (Found: C, 51·6; H, 4·9; N, 5·7. $C_{11}H_{13}O_4NS$ requires C, 51·8; H, 5·1; N, 5·5%). Attempts to prepare the free acid yielded the lactone.

N-p-*Toluenesulphonyl*-N-*β-hydroxypropylglycine* (VI), obtained from (IV) on treatment with *p*-toluenesulphonyl chloride and sodium hydroxide, crystallised from hot water in transparent prisms, m. p. 138—139° (Found: C, 49·9; H, 5·9; N, 5·2; S, 11·6. $C_{12}H_{17}O_5NS$ requires C, 50·2; H, 5·9; N, 4·9; S, 11·2%). On drying in a vacuum at 120° for 8 hours it lost one equivalent of water and gave N-p-*toluenesulphonyl*-6-*methyl*-2-*morpholone* (VII). This crystallised from benzene–light petroleum in colourless needles, m. p. 92—93° (Found: C, 53·7; H, 5·6. $C_{12}H_{13}O_4NS$ requires C, 53·5; H, 5·6%). Lactonisation was also effected by treatment of (VI) with acetic anhydride (no acetyl compound was produced), thionyl chloride, or even boiling benzene. No other derivative of the new amino-acid has been obtained crystalline.

Hydration of (II).—0·5 G. was slowly stirred into 2 c.c. of concentrated sulphuric acid and after ½ hour the mixture was poured on ice. The oil obtained solidified on scratching; after crystallisation from hot water it had m. p. and mixed m. p. with (VI) 139°. The mother-liquors from the crystallisation of (VI) yielded a little (VII), m. p. 93°. The filtrate from the collection of the crude (VI) in the above hydration gave a mixture of 2 : 4-dinitrophenylhydrazones which could not be separated by crystallisation. The m. p. (137°) suggested a mixture of acetone- and propaldehyde-2 : 4-dinitrophenylhydrazones.

Compound (I) was similarly hydrated to the lactone (V).

Condensation of β-Hydroxypropylamine with Ethyl Bromoacetate.—The amine (Levene and Watt, *J. Biol. Chem.*, 1926, **71**, 461) was characterised as its *phenylcarbamyl* derivative [presumably $CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}NHPh$], which was prepared by treating the amine (1 mol.) slowly with phenylcarbimide (1 mol.) at 0°. The mixture became glass-like and solidified on elutriation with benzene. It crystallised from ethyl acetate–benzene in colourless plates, m. p. 108—109° (Found: C, 62·2; H, 6·9. $C_{10}H_{14}O_2N_2$ requires C, 61·9; H, 7·2%). The *phenylurethane* of the phenylcarbamyl derivative was obtained by heating the latter with an excess of phenylcarbimide for ½ hour on the water-bath. After cooling, the mixture was repeatedly stirred with benzene, and the solid collected. It crystallised from ethyl acetate–benzene in clusters of colourless needles, m. p. 180—181° (Found: C, 65·0; H, 5·8. $C_{17}H_{19}O_3N_3$ requires C, 65·2; H, 6·1%).

β-Hydroxypropylamine (2 g.), cooled to 0°, was slowly treated, with stirring, with ethyl bromoacetate (2·2 g.). After 12 hours the mixture was poured into water, unchanged ester extracted with ether, and the aqueous solution just acidified to Congo-red with hydrochloric acid and heated on the water-bath for 1 hour. Hydrochloric acid was removed by silver oxide, silver by hydrogen sulphide, and the filtrate decolourised (charcoal) and evaporated to a syrup in a vacuum. It was stirred several times with acetone to remove the excess of β-hydroxypropylamine and once with methyl alcohol. The solid obtained crystallised from methyl alcohol–acetone in colourless rectangular prisms, m. p. 194—195° (Found: C, 45·4; H, 7·9%). It gave no depression in m. p. with compound (IV), and its *p*-toluenesulphonyl derivative was identical with (VI).

Oxidation of β-Hydroxypropylglycine.—Iodine (1·2 g.) was added to a solution of sodium carbonate (1·2 g.) and the amino-acid (0·2 g.) in 10 c.c. of water and the mixture was gently warmed for 10 minutes, cooled, and extracted with ether. From the ethereal solution, iodoform (0·05 g.), m. p. 119—120°, was isolated, but the other oxidation product (iminodiacetic acid) was not obtained crystalline.

N-*Benzenesulphonyl*-N-*β-methylallylglycine* (VIII).—A mixture of benzenesulphonylglycine (3 g.) in 3N-sodium hydroxide (25 c.c.) and β-methylallyl chloride (20 g.) was refluxed on the water-bath for 9 hours. The mixture was steam-distilled, cooled, treated with charcoal, and filtered. The well-stirred solution was acidified at 0°, and the product washed and dried. It crystallised from benzene–light petroleum (charcoal) in colourless prisms (3 g.), m. p. 91—92°. For analysis it was dried at 80° in a vacuum (Found: C, 53·9; H, 5·8. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%).

N-p-*Toluenesulphonyl*-N-*β-methylallylglycine* (IX), prepared in the same manner, crystallised from benzene in needles, m. p. varying from 92 to 106° according to the rate of heating. After being heated for 5 hours at 80° in a vacuum, it had m. p. 109—110° (Found: C, 55·0; H, 6·3. $C_{13}H_{17}O_4NS$ requires C, 55·1; H, 6·0%). The unheated crystals yielded benzene when warmed with water, indicating the presence of benzene of crystallisation. 5 G. of compound (IX), esterified with alcoholic hydrogen chloride, yielded 3 g. of product which crystallised from light petroleum in long silky needles, m. p. 67·5—68°. It contained bound chlorine and on treatment with dilute aqueous sodium hydroxide gave a solution containing sodium chloride. On acidification this yielded the lactone (XII). The ester was therefore *ethyl* N-p-*toluenesulphonyl*-N-*β-chloroisobutylaminoacetate* (X) (Found: C, 51·8; H, 6·5. $C_{15}H_{22}O_4NClS$ requires C, 51·9; H, 6·3%).

N-*Benzenesulphonyl*-6 : 6-*dimethyl*-2-*morpholone* (XI).—*N*-Benzenesulphonyl-*N*-β-methylallylglycine (0·5 g.) was hydrated with concentrated sulphuric acid (2 c.c.) at 0°; after ½ hour the mixture was poured on ice, and the crude morpholone collected. The combined aqueous filtrates were retained. The *morpholone* crystallised from hot water in long, felted, colourless needles (0·35 g.), m. p. 134—135° (Found: C, 53·9; H, 5·7. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%). It dissolved slowly in sodium hydroxide, but was insoluble in sodium carbonate solution.

The filtrates were treated with 2 : 4-dinitrophenylhydrazine, and the hydrazone collected. After crystallisation from alcohol it had m. p. and mixed m. p. with *iso*butaldehyde-2 : 4-dinitrophenylhydrazone 182° (Lindenbaum, *J. Amer. Chem. Soc.*, 1930, **52**, 2955, gives m. p. 182°; Ostertag, *ibid.*, 1932, **54**, 3758, gives m. p. 187°) (Found: C, 47·7; H, 4·6. Calc. for $C_{10}H_{12}O_4N_4$: C, 47·6; H, 4·6%).

N-p-*Toluenesulphonyl*-6 : 6-*dimethyl*-2-*morpholone* (XII), prepared similarly, formed long felted needles, m. p. 133—134° (Found: C, 55·3; H, 5·9. $C_{13}H_{17}O_4NS$ requires C, 55·1; H, 6·0%).

Ozonolysis of N-*Benzenesulphonyl*-N-*β-methylallylglycine.*—The compound (1·5 g.) in chloroform (25 c.c.) was ozonised as in the case of the allyl analogue. The formaldehyde–dimedon product had m. p. 188—189°. The residue from the steam-distillation was cooled and extracted with ether, from which N-*benzenesulphonyl*-N-*acetonylglycine* (1 g.) was obtained. This, crystallised from ethyl acetate–light petroleum and then from water, formed stout, colourless prisms, m. p. 123° (Found: C, 48·9; H, 5·0. $C_{11}H_{13}O_5NS$ requires C, 48·7; H, 4·8%). On treatment with iodine and sodium carbonate, iodoform was produced. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in golden felted needles and behaved as though it contained water of crystallisation (Found: C, 45·9; H, 4·4. $C_{17}H_{17}O_8N_5S,H_2O$ requires C, 46·3; H, 4·3%).

Hydrolysis of N-*Benzenesulphonyl*-6 : 6-*dimethyl*-2-*morpholone.*—A suspension of this compound (10 g.) in 60% sulphuric acid (18·8 c.c. of concentrated acid, 23·4 c.c. of water) was refluxed for 4 hours; the vapour, passed into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride, gave *iso*butaldehyde-2 : 4-dinitrophenylhydrazone, m. p. 178°. From the hydrolysis liquor, glycine was isolated, identical with an authentic specimen, as also were the benzenesulphonyl and the phenylcarbamyl derivative.

N-*Mesitylenesulphonyl*-N-*β-methylallylglycine* (XIV).—The preparation from mesitylenesulphonylglycine in 2N-sodium hydroxide and β-methylallyl chloride, though it gave the desired *glycine* in colourless prisms, m. p. 117—118° (Found: C, 57·4; H, 7·0. $C_{15}H_{21}O_4NS$ requires C, 57·9; H, 6·8%), was unsatisfactory for the preparation of large batches and the following method was preferred. *Ethyl mesitylenesulphonamidoacetate* (XV) [large flat prisms, m. p. 43—44°, from benzene–light petroleum (Found: C, 52·5; H, 6·7. $C_{13}H_{19}O_4NS$ requires C, 52·2; H, 6·4%)] (10·7 g.) in alcohol (30 c.c.) was added to sodium ethoxide from sodium (0·8 g.) and alcohol (20 c.c.), followed by β-methylallyl chloride (4·3 g.), and the mixture was refluxed overnight. Alcohol was removed, the residue poured into water and extracted with ether, and the extract washed with dilute sodium hydroxide solution and with water and dried. The solvent was removed, and the residue hydrolysed with 10% methyl-alcoholic potash (50 c.c.), poured into water, and acidified. The solid obtained crystallised from dilute alcohol in colourless prisms (3·7 g.), m. p. 117—118°. Mesitylenesulphonylglycine was obtained from the alkaline extract.

N-*β-Hydroxyisobutylglycine* (XVI).—The compound (XIV) (20 g.) was refluxed for 4 hours with 50 c.c. of glacial acetic acid and 65 c.c. of concentrated hydrochloric acid, the mixture evaporated to dryness in a vacuum, and the residue dissolved in water and extracted with ether. The aqueous solution was evaporated to dryness in a vacuum, the remaining hydrochloric and sulphuric acids removed with litharge, followed by silver oxide, and lead and silver removed with hydrogen sulphide. From the filtrate a syrup was obtained which solidified on trituration with acetone and crystallised

from alcohol–ether in long needles, m. p. 176° (decomp.) (Found: C, 48·9; H, 9·1; N, 9·2. $C_6H_{13}O_3N$ requires C, 49·0; H, 8·8; N, 9·5%). The *p*-toluenesulphonyl compound prepared from it gave no depression in m. p. with (XII).

Condensation of β-hydroxy*iso*butylamine (5 g.) in alcohol (5 c.c.) with ethyl bromoacetate (4·7 g.) in alcohol (5 c.c.) at 0° gave after 2 days a solution from which, after removal of the excess of bromo-ester with ether and of hydrochloric acid with silver oxide, the required amino-acid was obtained in small yield, m. p. 176°, identical in all respects with (XVI). The new amino-acid is hygroscopic, gives a deep blue coloration with copper acetate, and has a sweet taste.

Attempts to prepare Inactive N-*β-Hydroxypropylalanine.*—Benzenesulphonylalanine (Cocker and Harris, *loc. cit.*), when treated with allyl bromide, gave a mixture (m. p. 102—119°) which could not be separated by crystallisation. However, since on hydration the required compound was expected to give a lactone, 2·5 g. of the above mixture were treated at 0° with 9 c.c. of concentrated sulphuric acid and the mixture was poured on ice and slowly basified with sodium carbonate. The precipitated *N-benzenesulphonyl-3 : 6-dimethyl-2-morpholone* (XVII), after being washed and dried, crystallised from benzene–light petroleum in colourless micro-prisms (Found: C, 53·65; H, 5·5. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%). Propaldehyde also was identified in the mixture. The following method proved more satisfactory. *Ethyl benzenesulphonyl-α-aminopropionate* (32 g.) [colourless flat prisms, m. p. 61—62°, from light petroleum–benzene (Found: C, 51·7; H, 5·8. $C_{11}H_{15}O_4NS$ requires C, 51·4; H, 5·8%)], dissolved in alcohol (150 c.c.), was added to a solution of sodium (2·9 g.) in alcohol (50 c.c.) and allyl chloride (11·4 g.; 1·2 mols.) and the mixture was refluxed for 8 hours. Alcohol was removed, and the residue poured into dilute sodium hydroxide solution and extracted with ether. From the ether an oil (18 g.) was obtained, which was hydrolysed on the water-bath with 10% alcoholic potash during 3 hours; the mixture was poured into water and acidified, and the oil obtained was extracted with ether. From the extract a solid was obtained, crystallisation of which from benzene–light petroleum yielded *N-benzenesulphonyl-N-allylalanine* (XVIII) in colourless prisms (about 8 g.), m. p. 95° (Found: C, 53·7; H, 5·5. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%). 5·5 G. of (XVIII) were hydrolysed with 60% sulphuric acid (5·8 c.c. of acid, 7·1 c.c. of water); from the mixture a brown syrup of the required amino-acid was obtained, which gave a deep blue coloration with copper acetate.

Condensation of β-Hydroxypropylamine with Ethyl α-Bromopropionate.—The bromo-ester (1·8 g.) was added to a cooled solution of the amine (3 g.) in alcohol (20 c.c.); after 2 days the alcohol was removed, and the residue poured into water (20 c.c.) and extracted with ether. The aqueous solution was warmed with barium hydroxide for 1 hour and evaporated to dryness in a vacuum; the residue was dissolved in water, and barium removed by sulphuric acid, the excess of acid by litharge, and lead by hydrogen sulphide. The final solution was evaporated to dryness in a vacuum, leaving a syrup which became solid on trituration with acetone; on crystallisation from alcohol and ether *β-hydroxypropylalanine* was obtained in small colourless prisms, m. p. 214° (Found: C, 48·6; H, 8·9. $C_6H_{13}O_3N$ requires C, 49·0; H, 8·8%). The yield was very small. The benzenesulphonyl compound prepared from it was identical with (XVII).

The following compounds were prepared in unsuccessful efforts to obtain the above amino-acid: *Ethyl* p-*toluenesulphonyl-α-aminopropionate* crystallised from benzene–light petroleum in large colourless prisms, m. p. 66—67° (Found: C, 51·4; H, 6·0. $C_{12}H_{17}O_4NS$ requires C, 53·1; H, 6·3%), *mesitylenesulphonylalanine* from benzene in needles, m. p. 155—156° (Found: C, 53·1; H, 6·3. $C_{12}H_{17}O_4NS$ requires C, 53·1; H, 6·3%), and its *ethyl* ester from alcohol in large colourless prisms, m. p. 99° (Found: C, 56·5; H, 7·2. $C_{14}H_{21}O_4NS$ requires C, 56·2; H, 7·0%).

Bromination Experiments.—N-*Benzenesulphonyl*-N-*βγ-dibromopropylglycine* (XIX). Bromine (0·5 g.) in chloroform (5 c.c.) was slowly added to a stirred solution of *N*-benzenesulphonyl-*N*-allylglycine (0·5 g.) in chloroform (15 c.c.) at 0° and after 1 hour the mixture was washed with dilute sodium bisulphite solution and with water and dried over sodium sulphate. From the solution an oil was obtained which crystallised from benzene–light petroleum in colourless needles, m. p. 117—118° after drying at 80° in a vacuum (Found: C, 31·9; H, 3·4. $C_{11}H_{13}O_4NSBr_2$ requires C, 31·8; H, 3·1%). This compound retained solvent very tenaciously. The *methyl* ester (XX), prepared from (XIX), crystallised from methyl alcohol in long colourless needles, m. p. 101—102° (Found: C, 33·2; H, 3·4. $C_{12}H_{15}O_4NSBr_2$ requires C, 33·6; H, 3·5%). The *ethyl* ester, prepared from (XIX) and alcoholic hydrogen chloride or by bromination of (III), crystallised from alcohol in micro-needles, m. p. 72° (Found: C, 35·5; H, 4·0. $C_{13}H_{17}O_4NSBr_2$ requires C, 36·2; H, 3·8%). N-p-*Toluenesulphonyl*-N-*βγ-dibromopropylglycine* (XXII) crystallised from benzene–light petroleum in transparent prisms, m. p. 127—128° after drying at 80° in a vacuum (Found: C, 34·0; H, 3·4; Br, 37·7. $C_{12}H_{15}O_4NSBr_2$ requires C, 33·6; H, 3·5; Br, 37·5%).

Reduction of the bromo-compounds. Compound (XIX) (1 g.) in methyl alcohol (25 c.c.) was reduced with hydrogen in the presence of Raney nickel. From the alcohol a solid was obtained which crystallised from benzene–light petroleum in colourless prisms, m. p. 102°, not depressed by authentic *N*-benzenesulphonyl-*N*-propylglycine.

Compound (XXII) (1 g.) in 20 c.c. of glacial acetic acid was heated on the water-bath for 4 hours with zinc dust (5 g.). After filtration the acetic acid was removed in a vacuum, and the residue poured into water. The oil obtained solidified on scratching and crystallised from benzene in needles (0·4 g.), m. p. 111·5°, not depressed by *N-p*-toluenesulphonyl-*N*-allyglycine (Found: C, 53·7; H, 5·9. Calc. for $C_{12}H_{15}O_4NS$: C, 53·5; H, 5·6%).

Hydrolysis of N-p-*Toluenesulphonyl*-N-*βγ-dibromopropylglycine.*—20 G., dissolved in 200 c.c. of 5% sodium hydroxide solution, were heated on the water-bath for 3 hours, cooled, and acidified. At the moment when the solution became acid to Congo-red the smell of acraldehyde developed (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 165°) and a solid was deposited. This, crystallised from ethyl acetate, had m. p. and mixed m. p. with *p*-toluenesulphonylglycine 147°. From the ethyl acetate, by concentration and crystallisation from alcohol, a small quantity of colourless needles, m. p. 193°, was obtained. This compound was readily soluble in dilute sodium bicarbonate solution, readily decolourised bromine in acetic acid, and on treatment with hot dilute sulphuric acid immediately gave an odour reminiscent of a mixture of acraldehyde and propaldehyde (Found: C, 41·4; H, 3·9; Br, 23·3. $C_{12}H_{14}NSBr$ requires C, 41·4; H, 4·0; Br, 23·3%). Ozonolysis yielded a volatile compound which gave a 2 : 4-dinitrophenylhydrazone, m. p. 156° (Found: C, 40·0; H, 3·2. Calc. for $C_9H_8O_8N_4$: C, 40·0; H, 3·3%). This corresponds to the 2 : 4-dinitrophenylhydrazone of glycollaldehyde, m. p. 155—156° (corr.) (Collatz and Neuberg, *Biochem. Z.*, 1932, **255**, 27).

N-m-*Nitrobenzenesulphonylglycine* (XXIII).—A well-agitated solution of glycine (5 g.) in N-sodium hydroxide (200 c.c.) was treated at intervals during 4 hours with a solution of *m*-nitrobenzenesulphonyl chloride in benzene, until 15 g. of the chloride had been added. The aqueous layer was acidified, and the precipitate crystallised from ethyl acetate–ligroin, forming colourless hairy needles (8 g.), m. p. 149—150° (Found: C, 37·1; H, 3·2. $C_8H_8O_6N_2S$ requires C, 36·9; H, 3·1%). The *ethyl* ester (XXIV), prepared in the presence of concentrated sulphuric acid, crystallised from alcohol in long needles, m. p. 122° (Found: C, 41·7; H, 4·6. $C_{10}H_{12}O_6N_2S$ requires C, 41·7; H, 4·2%).

Ethyl N-m-*Nitrobenzenesulphonyl-N-allylaminoacetate.*—Compound (XXIV) (3 g.) was heated on the water-bath with a mixture of sodium ethoxide (from 0·24 g. of sodium and 20 c.c. of alcohol) and allyl chloride (1 c.c.) for 6 hours. Alcohol was removed, the residue poured into water containing a little sodium hydroxide, and the solid collected, washed, and dried. It crystallised from alcohol in colourless needles or prisms, m. p. 57·5—58° (Found: C, 47·6; H, 5·1. $C_{12}H_{16}O_6N_2S$ requires C, 47·6; H, 49%). The *dibromide* crystallised from alcohol in colourless tufts, m. p. 91—91·5° (Found: C, 33·0; H, 3·5. $C_{12}H_{16}O_6N_2SBr_2$ requires C, 32·9; H, 3·4%).

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98. *The Decomposition of Diazo-compounds in Neutral Solution. Some Observations on the Diazo-coupling Reaction.*

By Herbert H. Hodgson and Ewart Marsden.

Aqueous solutions of diazotised amines, when maintained neutral by the presence of calcium carbonate, decompose to form bis- or mono-arylazophenols, aniline and *o*-toluidine giving the former, and *p*-toluidine, *o*-, *m*-, and *p*-nitroaniline, and α- and β-naphthylamine the latter. An aqueous solution of the equilibrium mixture $C_6H_5\cdot N{:}N\cdot OH \rightleftharpoons C_6H_5\cdot \overset{\oplus}{N}{:}N\}\overset{\ominus}{O}H$ decomposes to form nearly equal parts of 2 : 4-bisbenzeneazo- and 4-benzeneazo-phenol. The results are held to indicate that undissociated benzenediazohydroxide and not benzenediazonium hydroxide is the coupling component.

When aniline is diazotised in hydrochloric acid, and the solution then rendered exactly neutral with calcium carbonate and filtered, the filtrate rapidly decomposes with formation of phenol, hydrochloric acid, and a small amount of tar. A somewhat similar result is obtained when sulphuric acid and barium carbonate are used; the neutralised solution then develops sulphuric acid with formation of phenol, and about 40% of 2 : 4-bisbenzeneazophenol. If, however, the neutralised solution is allowed to decompose in the presence of calcium carbonate, an almost quantitative yield of 2 : 4-bisbenzeneazophenol results. The same reactions were afforded by *o*- and *p*-toluidine, *viz.*, formation of the cresol, mineral acid, and tar when the neutralised solutions decomposed in the absence of calcium carbonate, but of 3 : 5-bis-*o*-tolueneazo-*o*-cresol and 3-*p*-tolueneazo-*p*-cresol when it was present. When, however, neutralised diazo-solutions from *o*- or *m*-nitroaniline or α-naphthylamine were allowed to decompose *per se*, a *p*-arylmonoazophenol resulted even in the presence of the free mineral acid developed, and an *o*-arylmonoazophenol or naphthol was obtained when *p*-nitroaniline or β-naphthylamine was so treated. In all these cases a certain amount of tar was also present, but when the decompositions took place in conjunction with calcium carbonate, clean products were obtained.

Previous work (Hirsch, *Ber.*, 1890, **23**, 3705) on the decomposition of benzenediazonium sulphate in acid solution has shown that a small quantity of 4-hydroxydiphenyl is also formed. Further, it is stated (Saunders, "The Aromatic Diazo-Compounds and their Technical Applications," 1936, p. 68) that the products of decomposition of diazo-salts in aqueous solution do not interfere with the reaction except in the naphthalene series, in which the naphthols which are formed remove the diazo-compound by coupling when they have reached a certain concentration; also (p. 69) that the decomposition is not affected by the amount of free mineral acid present. These statements are now found to require qualification.

The mechanism for the decomposition reactions suggested by the present experiments is that the aryldiazonium chloride (*a*) is involved in a solvolytic reaction with water (cf. Hammett, "Physical Organic

$$\underset{(a)}{R\cdot\overset{\oplus}{N}{\equiv}N{:}\}\overset{\ominus}{Cl}} + H_2O \rightleftharpoons \underset{+\overset{\oplus}{H}+\overset{\ominus}{Cl}}{R\cdot\overset{\oplus}{N}{\equiv}N{:}\}\overset{\ominus}{O}H} \ (b) \rightleftharpoons \underset{(c)}{R\cdot N{=}\overset{\delta+}{N}{-}\overset{\delta-}{O}H}$$

Chemistry," McGraw-Hill Book Co., 1940, p. 167) in which the incipient solvation of the halide ion is the driving force of the reaction, and the diazonium ion is, in consequence, involved in a reversible reaction with water to give an equilibrium mixture of diazonium hydroxide (*b*) and diazo-hydroxide (*c*) (cf. Hammett, *op. cit.*, p. 295). Subsequent decomposition of (*b*) into phenol then occurs, together with a small amount of more profound decomposition, affording the tar. When the hydrochloric acid is removed by means of calcium carbonate as rapidly as it is formed, the phenol resulting from the decomposition of (*b*) couples with the diazohydroxide (*c*) to give an azo-compound. To test the latter view, aniline was diazotised in hydrochloric acid solution by nitrous fumes to ensure that no metal was present (*e.g.*, sodium or potassium), since in the subsequent operations this would render the solution alkaline; the diazo-solution was then shaken with excess of silver oxide and filtered. The filtrate, which could now only contain the equilibrium mixture of (*b*) and (*c*), and in the ratio 3—4 : 6—7 (Hantzsch and Davidson, *Ber.*, 1898, **31**, 1612), rapidly decomposed and deposited a mixture of approximately equal parts of 2 : 4-bisbenzeneazo- and 4-benzeneazo-phenol (whereas Hantzsch, *ibid.*, p. 340, reports a little phenol and much tar). If phenol or α-naphthol is added to the filtrate from the silver oxide treatment, rapid and ultimately quantitative precipitation of 4-benzeneazo-phenol or -1-naphthol occurs, the rate of formation of the latter being somewhat greater than that of the former. The solution of the above equilibrium mixture is deep yellow, and, contrary to Hantzsch (*loc. cit.*), is only slightly alkaline, *viz.*, to methyl-orange and litmus, but not to phenolphthalein and brilliant-yellow. When this solution was treated with acetic acid in excess, a complex decomposition occurred and some phenol and diphenyl were isolated from the tar, a reaction in striking contrast to the clean decomposition of the solution alone.

We conclude from these experiments in neutral solution, where the equilibrium (*b*) $\rightleftharpoons$ (*c*) is uninfluenced by external acid or base, that the coupling takes place between the diazohydroxide (*c*) and the phenolic compounds, whether formed by the decomposition of the diazonium hydroxide (*b*) or by addition to the equilibrium mixture. This view is in harmony with that of Conant and Peterson (*J. Amer. Chem. Soc.*, 1930, **52**, 1220) and also with the reactions of diazonium and diazo-compounds which involve respectively the scission and the retention of nitrogen.

Of all the amines diazotised, only aniline and *o*- and *p*-toluidine failed to couple in the presence of the mineral

acid developed when their diazo-solutions decomposed *per se*, and this acid amounted ultimately in the cases of both hydrochloric and sulphuric acid to *ca.* 60% of the theoretical amount expected if all the diazo-solution had been converted into phenol. The neutralised (calcium carbonate) solution of diazotised aniline or α-naphthylamine also failed to couple with phenol but did so with α-naphthol; whereas that from *p*-nitroaniline coupled at once with phenol.

Experimental.

General Procedure.—The amine (0·1 g.-mol.), dissolved in hydrochloric acid (24 c.c., *d* 1·16) and water (200 c.c.), was diazotised at 0° by addition of a solution of sodium nitrite (7 g.) in the minimum amount of water. The mixture was kept at 0° and neutralised with calcium carbonate (2—3 g.), filtered, and the clear solution stirred with calcium carbonate (6 g.). The mixture was allowed to decompose at room temperature during 3 days, being tested periodically to ensure that neutrality had been maintained; it was then heated at 70° for 4—5 hours for decomposition to become complete, as shown by addition of a drop to alkaline H-acid solution. The reaction mixture was then acidified with hydrochloric acid, filtered, and the precipitate of azo-compound washed with water and dried. The table gives the detailed results for eight representative amines.

Table of Decomposition Products.

Amine diazotised.	Weight taken, g.	Weight of azo-product, g.	Azo-product formed.
(1) Aniline	9·3	9·0	2 : 4-Bisbenzeneazophenol
(2) *o*-Toluidine	10·5	11·0	3 : 5-Bis-*o*-toleneazo-*o*-cresol
(3) *p*-Toluidine	10·5	10·5	3-*p*-Toleneazo-*p*-cresol
(4) *o*-Nitroaniline	13·8	14·0	2-Nitro-4-*o*-nitrobenzeneazophenol
(5) *m*-Nitroaniline	13·8	14·0	3-*Nitro*-4-*m*-*nitrobenzeneazophenol*
(6) *p*-Nitroaniline	13·8	13·1	4-*Nitro*-2-*p*-*nitrobenzeneazophenol*
(7) α-Naphthylamine	14·3	14·5	4-Naphthaleneazo-1-naphthol
(8) β-Naphthylamine	14·3	13·7	1-Naphthaleneazo-2-naphthol

Crystal description, analyses, and references. (1) Dark brown plates from ethyl alcohol, m. p. 124—125° (Ponzio, *Gazzetta*, 1913, **43**, i, 561, gives m. p. 123°) (Found: N, 18·7. Calc.: N, 18·6%). (2) Brown plates from cellosolve, m. p. 146° (Ponzio, *loc. cit.*, gives m. p. 146°) (Found: N, 16·2. Calc.: N, 16·3%). (3) Red plates from glacial acetic acid, m. p. 113° (Noelting and Kohn, *Ber.*, 1884, **17**, 304, give m. p. 112—113°) (Found: N, 12·4. Calc.: N, 12·4%). (4) Maroon needles from cellosolve, m. p. 190° (Hewitt and Mitchell, J., 1905, **87**, 226, give m. p. 186°) (Found: N, 19·6. Calc.: N, 19·5%). (5) Dark red plates from glacial acetic acid, m. p. 202° (Found: N, 19·4. $C_{12}H_8O_5N_4$ requires N, 19·4%). (6) Yellow micro-plates from alcohol, m. p. 168° (Found: N, 19·2. $C_{12}H_8O_5N_4$ requires N, 19·4%). (7) Very dark red micro-plates from glacial acetic acid (Found: N, 9·3. Calc.: N, 9·4%). (8) Maroon micro-plates from glacial acetic acid, m. p. 179° (Meldola and Hanes, J., 1894, **65**, 836, give m. p. 178—179°) (Found: N, 9·4. Calc.: N, 9·4%).

The authors thank I.C.I. (Dyestuffs) Ltd. for gifts of chemicals.

Technical College, Huddersfield. [*Received, April 6th*, 1943.]

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99. *The Absorption Spectra of Some* m-*Substituted Phenols, and the Influence of Nucleophilic Substituents on Electronic Mobility.*

By Herbert H. Hodgson.

The ultra-violet aborption spectra of phenol and of eight *m*-substituted phenols have been measured in aqueous neutral, acid, and alkaline solution. The substituents were all *op*-directing, *i.e.*, electron-repelling, and their considerable effects on the electronic mobility are compared.

The ultra-violet aborption spectra of *m*-substituted phenols, $R{\cdot}C_6H_4{\cdot}OH$, where R = F, Cl, Br, I, OH, Me, OMe, OEt, have been measured in neutral, acid, and alkaline aqueous solution, and compared with the spectrum of phenol to ascertain the effect of electron-repelling substituents on the electronic mobility of phenol. Between 2200 A. and 3200 A. all nine compounds afforded only one absorption band (see graphs), and this is ascribed to the un-ionised molecule in each case, since the 3-halogeno-4-nitrosophenols (except 3-fluoro-4-nitrosophenol), owing to their more pronounced ionisations, afford two bands (Hodgson, J., 1937, 520), one at *ca.* 3000 A. corresponding to the un-ionised molecule, and the other at *ca.* 4000 A. due to the anion. 3-Fluoro-4-nitrosophenol has only band, due to the anion (Hodgson, this vol., p. 89).

The bands are really the envelopes of the fine structures not revealed in aqueous solution, and the peak displacements of all the *m*-substituted phenols (except *m*-fluorophenol) relative to that of phenol are towards the longer wave-lengths in neutral and acid solution. The peak of the *m*-fluorophenol band envelope is shifted by 30 A. towards a shorter wave-length. These shifts indicate a loosening of the electronic structure of phenol by the substituent except in the case of fluorine, which imposes a restraint. In alkaline solution, however, *m*-fluorophenol comes into line, owing to the increased ionisation and therefore decreased restraint in the un-ionised molecule.

The four *m*-halogenophenols have their shifts in the order, F < Cl < Br < I, *i.e.*, exactly the reverse of that of the total effects of the halogens as indicated by the ionisations of the phenols, except that *m*-fluorophenol is anomalous (Baddeley, Bennett, Glasstone, and Jones, J., 1935, 1827; Hodgson and Smith, J., 1939, 154).

In neutral and in acid solution the shifts for the remaining substituents are in the order, O > Me = OH = OMe, but in alkaline solution the order becomes OH > OEt > OMe > Me > H, which was to be anticipated, the second phenolic group in resorcinol being now more ionised and the structure of the molecule correspondingly loosened. This order illustrates clearly the differences in *op*-directing power of the groups, and is in accord with that established by their effects on chemical reactivity.

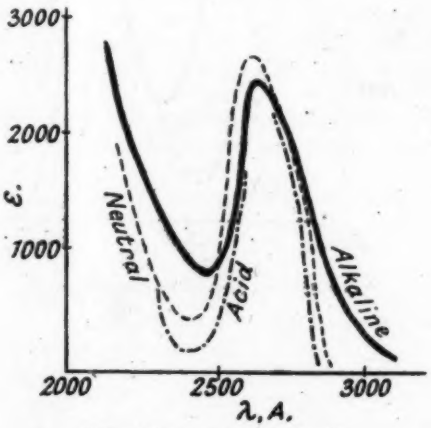
A comparison of the band-envelope shifts of all nine compounds gives : In neutral and in acid solutions, F < H < OH,Me,OMe,Cl < OEt < Br < I ; in alkaline solution, H < F < Me < OMe < OEt < OH < Cl < Br < I.

Experimental.

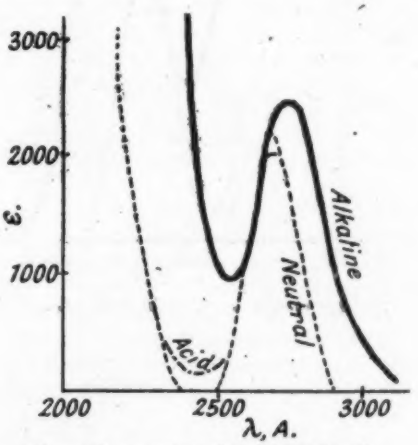
Apparatus and Measurements.—All measurements were made by means of a Hilger U.-V. Spekker Spectrophotometer, the absorption due to 1, 2, or 4 cm. paths being compared photographically with a blank cell filled with the solvent used. All the solutions were aqueous, in some cases with a trace of alcohol. Acidity was produced by hydrochloric acid, and alkalinity by sodium hydroxide. The pH measurements were made on a standard Cambridge pH meter.

Absorption Data.

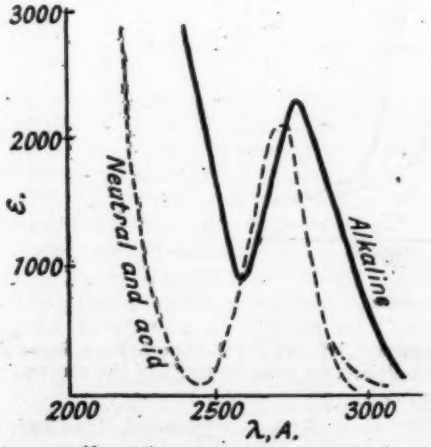
	Concn.		pH Values.			Acid and neutral solution.		Alk. soln.	
Compound.	Mg./l.	4N × 10^{-4}.	Acid.	Neutral.	Alk.	λ max., A.	λ min., A.	λ max., A.	λ min., A.
m-Fluorophenol	54·2	1·21	3·21	7·61	9·03	2680	2410	2755	2540
m-Chlorophenol	60·8	1·18	3·12	7·69	9·10	2740	2475	2880	2605
m-Bromophenol	62·8	0·91	3·11	7·70	10·17	2760	2475	2925	2690
m-Iodophenol	64·4	0·73	3·06	7·55	10·00	2770	2525	2970	2645
m-Cresol	54·6	1·27	2·64	7·61	9·93	2740	2450	2790	2570
m-Methoxyphenol	62·2	1·25	2·38	7·22	9·96	2740	2450	2825	2580
m-Ethoxyphenol	63·8	1·15	2·68	6·95	10·11	2755	2450	2847	2593
Phenol	33·5	0·81	3·75	7·00	9·21	2710	2410	2720	2490
Resorcinol	44·7	1·02	2·38	7·16	11·00	2740	2450	2870	2600



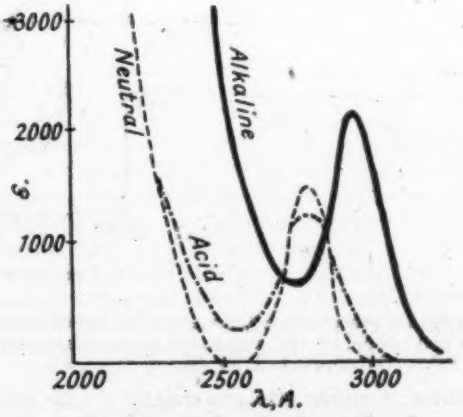
Absorption spectra of phenol.



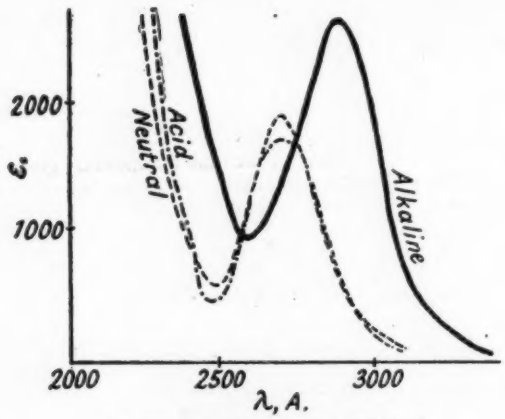
Absorption spectra of m-*fluorophenol.*



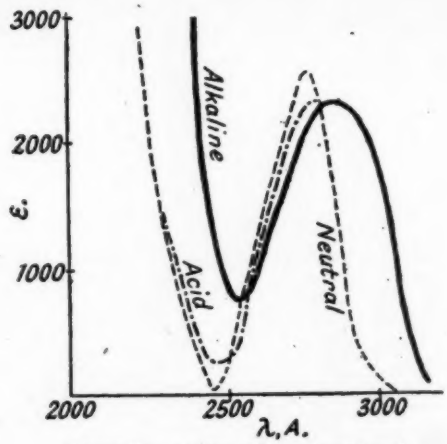
Absorption spectra of m-*cresol*



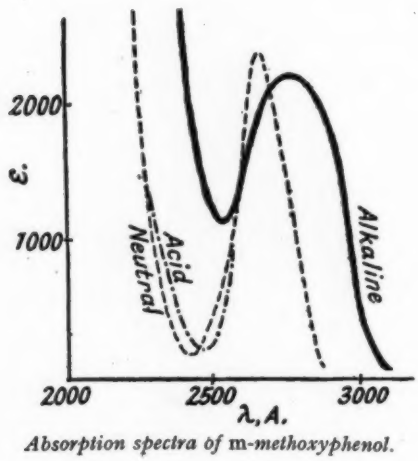
Absorption spectra of m-*bromophenol.*



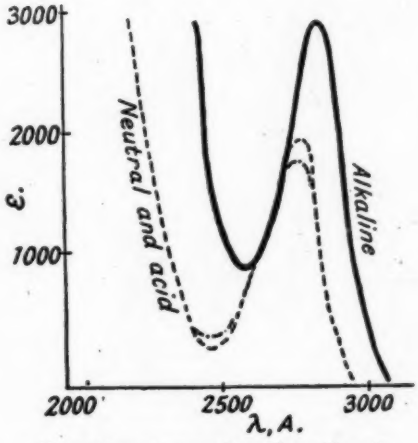
Absorption spectra of m-*iodophenol.*



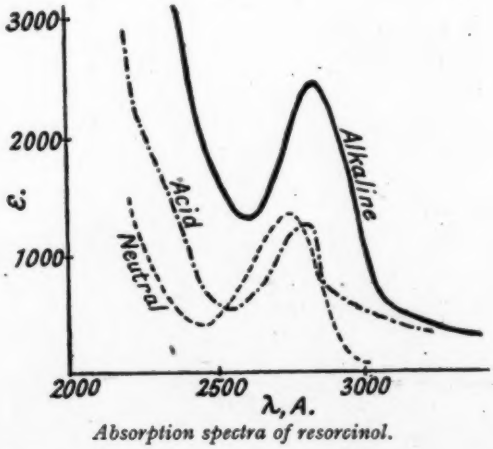
Absorption spectra of m-*chlorophenol.*



Absorption spectra of m-*methoxyphenol.*



Absorption spectra of m-*ethoxyphenol.*



Absorption spectra of resorcinol.

The author gratefully acknowledges his indebtedness to Dr. H. Lowery, Principal of the South-West Essex Technical College and School of Art, and to his research assistant, Mr. D. Price, B.Sc., for measurements of the spectra. He also thanks I.C.I. (Dyestuffs) Ltd. for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD.

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100. *Experiments on the Synthesis of Purine Nucleosides. Part I. Model Experiments on the Synthesis of 9-Alkylpurines.*

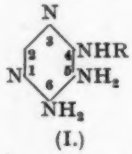
By J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd.

A series of model experiments is described, in which a hypothetical route to the synthesis of purine nucleosides is examined. The conversion of 4-amino-5-thioformamidopyrimidines into purines can be carried out by boiling in aqueous, pyridine or quinoline solution. As anticipated on theoretical grounds, similar treatment of *6-amino-4-methylamino-5-thioformamido-2-methylthiopyrimidine* yields exclusively *2-methylthio-9-methyladenine*, indicating a convenient route to the synthesis of 9-substituted 6-aminopurines. In the course of the work, a number of other new pyrimidine and purine derivatives have been prepared.

The importance of the purine nucleosides, not only as components of nucleic acids but also in the composition of enzyme systems concerned in vital processes, has become increasingly clear in recent years. Adenosine (9-*d*-ribofuranosidoadenine) (II; R = *d*-ribofuranose) is known to form an essential part of a number of co-enzymes concerned in the transfer of hydrogen and phosphate in biological systems, and we have for some time been engaged in experiments designed to test the possibility of a synthesis of this and other 9-glycosidopurines. A successful outcome of these experiments might, by rendering such substances available, further our knowledge of the relation between chemical structure and co-enzyme function.

Although it is now more than thirty years since the first purine nucleoside was isolated, no synthesis of a naturally occurring compound of this class has yet been reported, and it is only recently that the location of the sugar residue in them at N_9 has been established by a study of their ultra-violet absorption spectra (Gulland and Holiday, J., 1936, 765). Fischer and Helferich (*Ber.*, 1914, **47**, 210) prepared *d*-glucosides of adenine, guanine, and hypoxanthine from the reaction product of acetobromoglucose and trichloropurine silver, and, more recently, Gulland and Story (J., 1938, 259) have shown by spectroscopic methods, that the glucose residue in these compounds is in the N_9 position. The glycosidic grouping in these compounds is, however, of the pyranose type, whereas the natural nucleosides have a furanose structure. Although the synthetic method of these authors could doubtless be applied to the synthesis of, say, adenosine, it is rather limited in scope for our purposes, which involve the study of a wide range of adenosine analogues. Gulland and his collaborators have also investigated two other possible synthetic routes, either of which would provide unequivocal proof of the position of the glycosidic residue in the products. In the first of these (Gulland and Macrae, J., 1933, 662) an unsuccessful attempt was made to obtain theophylline 9-*d*-glucoside by condensing 1 : 3-dimethyluramil with tetra-acetylglucose *iso*thiocyanate; in the second (Allsebrook, Gulland, and Story, J., 1942, 232) efforts to synthesise a 9-glucosidopurine from an *N*-glucosidoglyoxaline failed owing to the inaccessibility of the appropriate glyoxaline derivative.

In our approach to the problem we envisaged a synthesis involving the preparation of a 5 : 6-diamino-4-glycosidaminopyrimidine (*e.g.*, I; R = *d*-ribofuranose), followed by conversion of this into the required 9-glycosidoadenine (*e.g.*, II; R = *d*-ribofuranose). This method is analogous to the well-known Traube synthesis of adenine (*Annalen*, 1904, **331**, 64), in which a compound of type (I; R = H) is heated with formic acid, the 5-formamido-derivative first produced cyclising at higher temperatures by loss of water. Owing to its ease of hydrolysis a 9-glycosidoadenine would in all probability be destroyed under such drastic reaction conditions if indeed it were formed at all. We therefore directed our attention in the first instance to the elaboration of a milder cyclisation procedure, employing as model substances sugar-free pyrimidine derivatives.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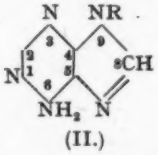
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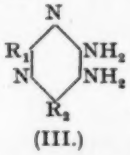
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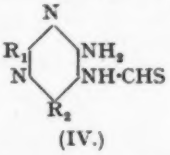
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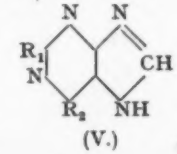
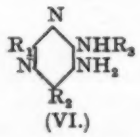

(V.)

A possible method for converting 4 : 5-diaminopyrimidines into purines under mild conditions was suggested by the observation of Todd, Bergel, and Karimullah (J., 1936, 1557) that 4 : 5-diamino-6-methylpyrimidine (III; R_1 = H, R_2 = Me) on treatment with aqueous potassium dithioformate yielded 4-amino-5-thioformamido-6-methylpyrimidine (IV; R_1 = H, R_2 = Me), which when heated above its m. p. readily evolved hydrogen sulphide, giving 6-methylpurine (V; R_1 = H, R_2 = Me). It has now been found that the conversion of 4-amino-5-thioformamidopyrimidines into purines can be brought about readily by boiling their solutions in water or anhydrous organic solvents such as pyridine or quinoline until evolution of hydrogen sulphide ceases; the generality of this method has been tested by application to the synthesis of a number of purines. On the whole the use of anhydrous organic solvents in the reaction is recommended, since in certain cases boiling with water leads to the production of considerable amounts of 5-formamidopyrimidine. 4 : 5-Diamino-6-hydroxy-2-methylpyrimidine (III; R_1 = Me, R_2 = OH), treated with aqueous sodium dithioformate, yielded the corresponding *5-thioformamido*-compound (IV; R_1 = Me, R_2 = OH), convertible into 6-hydroxy-2-methylpurine (V; R_1 = Me, R_2 = OH) on boiling with quinoline.

4 : 5 : 6-*Triamino-2-methylthiopyrimidine* (III; R_1 = SMe, R_2 = NH_2), prepared from 4 : 6-diamino-2-methylthiopyrimidine by treatment with nitrous acid and reduction of the resulting 5-nitroso-derivative

with ammonium sulphide, gave with sodium dithioformate 4 : 6-*diamino*-5-*thioformamido*-2-*methylthiopyrimidine* (IV; R_1 = SMe, R_2 = NH_2), cyclised to 2-*methylthioadenine* (V; R_1 = SMe, R_2 = NH_2). In similar fashion 4 : 6-*diamino*-5-*thioformamido*-2-*methylpyrimidine* (IV; R_1 = Me, R_2 = NH_2) yielded 2-*methyladenine* (V; R_1 = Me, R_2 = NH_2). The thioformamido-compound was in this case prepared from 4 : 6-dihydroxy-2-methylpyrimidine. The latter, on heating with phosphoryl chloride, gave 4 : 6-*dichloro*-2-*methylpyrimidine*, aminated successively to 4-chloro-6-amino-2-methylpyrimidine and 4 : 6-diamino-2-methylpyrimidine. Treatment of this diamine with dilute hydrochloric acid and sodium nitrite gave the 5-nitroso-derivative, which was reduced with ammonium sulphide and the crude product converted directly into (IV; R_1 = Me, R_2 = NH_2) by means of aqueous sodium dithioformate.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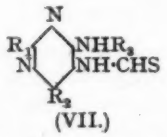
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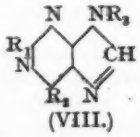
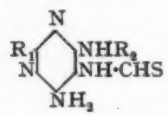
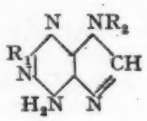

(VIII.)

We next applied the procedure described to the synthesis of 9-alkylpurines. On heating a quinoline solution of 4-*methylamino*-5-*thioformamido*-2-*hydroxy*-6-*methylpyrimidine* (VII; R_1 = OH, R_2 = R_3 = Me), ring-closure occurred readily, giving 2-*hydroxy*-6 : 9-*dimethylpurine* (VIII; R_1 = OH, R_2 = R_3 = Me). The ready cyclisation in this case was not unexpected, since Johns (*J. Biol. Chem.*, 1911, **9**, 161) observed that 5-amino-6-methylamino-2-hydroxypyrimidine reacted with formic acid to give the corresponding purine even more readily than 4 : 5-diamino-2-hydroxypyrimidine.

For the preparation of a 9-alkyladenine by this method a 6-amino-4-alkylamino-5-thioformamidopyrimidine is required and theoretically ring closure might occur in two ways, giving either a 9-alkylpurine (X) or a 6-alkylaminopurine (XI).


(IX.)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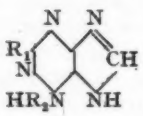
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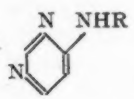
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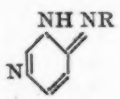
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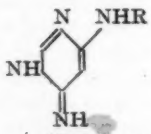
(XIV.)

It seemed to us probable that the ring closure would in fact lead to the production of the 9-alkylpurine (X). Our experience of the behaviour of pyrimidine derivatives suggested that a 4- or 6-alkylaminopyrimidine would tend to react more in the form (XII; R = alkyl) and less in the tautomeric iminodihydropyrimidine form (XIII ; R = alkyl) than would be the case with a 4- or 6-aminopyrimidine (XII and XIII; R = H), *i.e.*, a 4-alkylamino-6-aminopyrimidine would react as if it had structure (XIV). In this case cyclisation of (IX) by loss of hydrogen sulphide would be expected to lead to (X) rather than (XI). The ready cyclisation of 4-alkylamino-5-thioformamidopyrimidines already noted accords with this view.

In order to decide which type of reaction did, in fact, occur, we investigated the behaviour of 6-*amino*-4-*methylamino*-5-*thioformamido*-2-*methylthiopyrimidine* (IX; R_1 = SMe, R_2 = Me). 4-Chloro-6-amino-2-methylthiopyrimidine, reacting with methylamine, gave 6-*amino*-4-*methylamino*-2-*methylthiopyrimidine*, which was nitrosated, reduced, and the crude product thioformylated to give the required (IX; R_1 = SMe, R_2 = Me). When an aqueous solution of this compound was boiled till hydrogen sulphide evolution ceased, only one product could be isolated. This was identical with the product obtained when 2-methylthioadenine was methylated under the conditions described by Krüger (*Z. physiol. Chem.*, 1894, **18**, 434) for the conversion of adenine into 9-methyladenine; it is therefore to be regarded as the expected 2-*methylthio*-9-*methyladenine* (X; R_1 = SMe, R_2 = Me). In accordance with this view of its structure it underwent deamination with nitrous acid at 60°, giving 6-*hydroxy*-2-*methylthio*-9-*methylpurine* (2-*methylthio*-9-*methylhypoxanthine*). No evidence for the formation of a substance of type (XI) could be obtained.

If, as might be anticipated, a 4-glycosidamino-group in the pyrimidine nucleus behaves in similar fashion to a 4-methylamino-group, then the synthetic method described should be applicable to the preparation of 9-glycosidopurines of the adenosine type, since we have established that the cyclisation stage can be accomplished by boiling solutions of the 5-thioformamido-compounds in anhydrous solvents such as pyridine, thus avoiding the considerable risk of hydrolysis which would attend boiling in aqueous solution.

Experimental.

The sodium dithioformate used throughout was the crystalline hexahydrate, $H{\cdot}CS{\cdot}SNa,6H_2O$.

4-*Amino*-5-*thioformamido*-6-*hydroxy*-2-*methylpyrimidine* (IV; R_1 = Me, R_2 = OH).—4 : 5-Diamino-6-hydroxy-2-methylpyrimidine (25 g.) (Traube, *Annalen*, 1923, **432**, 287) was dissolved in water (1 l.) at 65°, aqueous sodium dithioformate (50 g. in 350 c.c. of water) added, and the solution cooled rapidly. A small amount of the pyrimidine separated but subsequently redissolved. After standing overnight, the *thioformyl* derivative which had separated was collected and recrystallised from warm water, forming colourless plates which decomposed slowly above 260° without melting (Found : C, 39·3; H, 4·2; N, 30·7. $C_6H_8ON_4S$ requires C, 39·1; H, 4·3; N, 30·4%). Yield, quantitative.

6-*Hydroxy*-2-*methylpurine* (2-*Methylhypoxanthine*) (V; R_1 = Me, R_2 = OH).—The above thioformamido-compound (3 g.) was refluxed with quinoline (30 c.c.) for ½ hour. Dissolution was followed by evolution of hydrogen sulphide and the

purine gradually separated. The solid was collected and recrystallised from hot water, forming colourless needles (2·7 g.) which decomposed above 360° [Found in material dried at room temperature over calcium chloride: C, 38·3; H, 5·5; N, 30·7; loss at 140° (P_2O_5), 20·0. Calc. for $C_5H_5ON_4,2H_2O$: C, 38·7; H, 5·4; N, 30·2; loss ($2H_2O$), 19·6%]. The properties of the compound agreed with those given by Traube (*Annalen*, 1923, **432**, 287) for 2-methylhypoxanthine.

4 : 5 : 6-*Triamino-2-methylthiopyrimidine* (II; R_1 = SMe, R_2 = NH_2).—A solution of 4 : 6-diamino-2-methylthiopyrimidine (10 g.) (Wheeler and Jamieson, *Amer. Chem. J.*, 1904, **32**, 349) in a mixture of water (500 c.c.) and glacial acetic acid (28 c.c.) was cooled in ice, and a similarly cooled solution of sodium nitrite (9·6 g. in 100 c.c. of water) added. After standing for 2 hours at 0°, the light blue nitroso-compound was collected, washed, suspended in water (100 c.c.), and reduced by adding ammonium sulphide solution (41 c.c. of 17% aqueous ammonia saturated with hydrogen sulphide at 0°). After the mixture had been shaken for 2 hours, the greenish precipitate of 4 : 5 : 6-*triamino-2-methylthiopyrimidine* was collected and recrystallised from water (charcoal), forming long needles (5 g.), m. p. 182° (Found: C, 34·9; H, 5·2. $C_5H_9N_5S$ requires C, 35·1; H, 5·3%).

4 : 6-*Diamino-5-thioformamido-2-methylthiopyrimidine* (IV; R_1 = SMe, R_2 = NH_2).—Sodium dithioformate (5·8 g.) was added to a solution of the above triamino-compound (3·7 g.) in water (450 c.c.) at 40°. After standing overnight, the *thioformyl* derivative was collected. It crystallised from hot water in faintly yellow, silky needles (3·5 g.), m. p. 235° (decomp.) (rapid heating) (Found: C, 33·4; H, 4·4; N, 32·5. $C_6H_9N_5S_2$ requires C, 33·5; H, 4·2; N, 32·6%).

2-*Methylthioadenine* (V; R_1 = SMe, R_2 = NH_2).—The above thioformamido-compound (3·4 g.) was boiled with water (200 c.c.) for 36 hours. The *purine* separated on cooling and was recrystallised from water (charcoal), forming colourless silky needles (2 g.), m. p. 290° (decomp.) (Found: C, 35·7; H, 4·6; N, 35·5. $C_6H_7N_5S,H_2O$ requires C, 36·2; H, 4·5; N, 35·2%). The same product was obtained on refluxing the thioformamido-compound with quinoline for 20 minutes.

4 : 6-*Dichloro-2-methylpyrimidine*.—A mixture of 4 : 6-dihydroxy-2-methylpyrimidine (20 g.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and phosphoryl chloride (140 c.c.) was refluxed till evolution of hydrogen chloride ceased (*ca.* 2 hours). The excess of phosphoryl chloride was removed in a vacuum, and the residual oil poured on ice. The solid product was collected, washed with water, and dried in a desiccator. After sublimation in a vacuum 4 : 6-*dichloro-2-methylpyrimidine* formed colourless needles, m. p. 48—49° (yield, 75%) (Found: Cl, 43·1. $C_5H_4N_2Cl_2$ requires Cl, 43·6%). This compound was first prepared by Mr. A. Parkinson in these laboratories in the course of other investigations.

4-*Chloro-6-amino-2-methylpyrimidine*.—The above dichloro-compound (1 g.) was heated in a sealed tube with saturated methyl-alcoholic ammonia (6 c.c.) at 130° during 3 hours. After removal of the solvent and recrystallisation from methanol the product formed colourless needles (0·5 g.), m. p. 190—191° (Found: C, 42·1; H, 4·3; N, 29·4; Cl, 25·4. Calc. for $C_5H_6N_3Cl$: C, 41·9; H, 4·2; N, 29·3; Cl, 24·8%). Földi, von Fodor, Demjén, Szekeres, and Halmos (*Ber.*, 1942, **75**, 755) give m. p. 189°.

4 : 6-*Diamino-2-methylpyrimidine*.—4 : 6-Dichloro-2-methylpyrimidine (1·6 g.) was heated in a sealed tube with saturated methyl-alcoholic ammonia (12 c.c.) at 200° for 4 hours. The cooled solution was filtered from ammonium chloride and evaporated, and the residue extracted with boiling *n*-butanol. The extract was evaporated under reduced pressure, and the residue dissolved in alcohol, shaken with a little aluminium oxide, filtered, and concentrated to small bulk. The *diamino*-compound separated on cooling in colourless needles, m. p. 294—295° (sealed tube). Yield, 75% (Found: C, 48·6; H, 6·7; N, 44·7. $C_5H_8N_4$ requires C, 48·5; H, 6·5; N, 45·1%). The substance was readily soluble in water and alcohol and formed a *picrate* crystallising from water in long yellow needles which on heating decomposed above 250° (Found: C, 37·5; H, 3·2; N, 27·6. $C_5H_8N_4,C_6H_3O_7N_3$ requires C, 37·3; H, 3·1; N, 27·7%).

4 : 6-*Diamino-5-thioformamido-2-methylpyrimidine* (IV; R_1 = Me, R_2 = NH_2).—To a solution of 4 : 6-diamino-2-methylpyrimidine (2 g.) in 3N-hydrochloric acid (25 c.c.) at 0°, ice-cold sodium nitrite (1·5 g. in 10 c.c. of water) was added. After 1 hour at 0° the pale blue nitroso-compound was collected; it showed no m. p. below 300°. Reduction was effected by suspending it in an ice-cold solution of ammonium sulphide (from 80 c.c. of 14% aqueous ammonia saturated at 0° with hydrogen sulphide) and shaking for 2 hours. The brownish solution was evaporated to dryness under reduced pressure, and the residue extracted with warm water. The extract was filtered, sodium dithioformate (6 g.) added, and the mixture kept overnight. The precipitated *thioformamido*-compound crystallised from hot water (charcoal) in colourless needles which had no definite m. p. (yield, 35%) (Found: C, 39·2; H, 4·6; N, 38·0; S, 17·1. $C_6H_9N_5S$ requires C, 39·4; H, 4·9; N, 38·2; S, 17·5%).

2-*Methyladenine* (V; R_1 = Me; R_2 = NH_2).—The above thioformyl derivative (10 g.) was refluxed with quinoline (100 c.c.) for 30 mins., during which time it passed into solution with evolution of hydrogen sulphide and the *purine* rapidly crystallised. After cooling, the product was collected, washed with alcohol, and purified by dissolution in dilute hydrochloric acid and precipitation with ammonia (yield, 75%). It was sparingly soluble in hot water, from which it crystallised in tiny plates which did not melt below 300° (Found: C, 48·3; H, 4·7; N, 47·1. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 47·0%). The cyclisation was very much slower in pyridine solution. The *picrate* crystallised from water in yellow needles decomposing above 250° (Found: C, 38·0; H, 2·6; N, 29·6. $C_6H_7N_5,C_6H_3O_7N_3$ requires C, 37·7; H, 2·6; N, 30·2%).

4-*Methylamino-5-thioformamido-2-hydroxy-6-methylpyridimine* (VII; R_1 = OH, R_2 = R_3 = Me).—Thioformylation of 5-amino-4-methylamino-2-hydroxy-6-methylpyrimidine (0·25 g.) (Johns, *J. Biol. Chem.*, 1912, **11**, 393) in the normal manner with sodium dithioformate (0·25 g.) yielded a *product* crystallising from water in colourless prisms (0·22 g.) which on heating evolved hydrogen sulphide but did not melt below 300° (Found: N, 28·0. $C_7H_{10}ON_4S$ requires N, 28·3%).

2-*Hydroxy-6* : 9-*dimethylpurine*.—The above thioformyl derivative (3·2 g.), refluxed with quinoline (50 c.c.) for 20 mins. and worked up in the usual manner, gave a *product* crystallising from water (charcoal) in needles which did not melt below 300° (Found: C, 51·0; H, 4·9; N, 34·6. $C_7H_8ON_4$ requires C, 51·2; H, 4·9; N, 34·1%).

6-*Amino-4-methylamino-2-methylthiopyrimidine* (VI; R_1 = SMe, R_2 = NH_2, R_3 = Me).—4-Chloro-6-amino-2-methylthiopyrimidine (1 g.) (Johnson and Johns, *Amer. Chem. J.*, 1905, **34**, 183) was heated in a sealed tube with aqueous methylamine (1·4 g. of 33%) at 100° for 3 hours. The crystalline solid which separated was recrystallised from water, forming colourless needles (0·75 g.), m. p. 143—144° (Found: C, 42·5; H, 5·8; N, 32·6; S, 18·3. $C_6H_{11}N_4S$ requires C, 42·4; H, 5·9; N, 33·0; S, 18·8%).

6-*Amino-4-methylamino-5-thioformamido-2-methylthiopyrimidine* (IX; R_1 = SMe, R_2 = Me).—6-Amino-4-methylamino-2-methylthiopyrimidine (4 g.) was dissolved in dilute acetic acid (50 c.c. of 10%) and treated at 0° with a concentrated aqueous solution of sodium nitrite (2 g.). After standing overnight, the pale blue nitroso-compound was collected (4 g., m. p. 236°), suspended in ammonium sulphide solution (from 20 c.c. of 17% aqueous ammonia saturated with hydrogen sulphide at 0°), and warmed to 35°; it then dissolved and a yellow solid began to separate. When no more separated, the mixture was evaporated under reduced pressure, and the residue extracted repeatedly with boiling water. To the combined extracts, sodium dithioformate (8 g.) was added and after standing overnight the *thioformyl* derivative was collected. Recrystallised from water at 70° (charcoal), it formed colourless needles (3·5 g.), m. p. 185—186° with evolution of hydrogen sulphide (Found: C, 36·7; H, 5·2; N, 30·4. $C_7H_{11}N_5S_2$ requires C, 36·6; H, 5·0; N, 30·6%).

2-*Methylthio-9-methyladenine* (X; R_1 = SMe, R_2 = Me).—(a) *From the above thioformamido-compound.* The substance (IX; R_1 = SMe, R_2 = Me) (3 g.) was boiled with water (100 c.c.) for 5 hours, separated solid brought into solution by adding more water, and after boiling with charcoal for a short time the mixture was filtered and cooled. Colourless needles

of 2-*methylthio*-9-*methyladenine* separated (Found: C, 43·2; H, 4·6; N, 36·4. $C_7H_9N_5S$ requires C, 43·0; H, 4·6; N, 35·9%). The product had m. p. 261—262°, undepressed on admixture with a specimen prepared by route (b) below. From the crystallisation mother-liquors further quantities of the same compound were obtained, the yield of purified product being 94%; no other substance was detected. Similar results were obtained when the thioformamido-compound was refluxed with pyridine or quinoline.

(b) *From* 2-*methylthioadenine*. 2-Methylthioadenine (0·36 g.) was refluxed with alcoholic sodium hydroxide (0·08 g. in 30 c.c. of alcohol) and methyl iodide (0·32 g.) for 1 hour and kept overnight at room temperature. The 2-methylthio-9-methyladenine which separated crystallised from water in colourless needles, m. p. 262—263°.

Deamination of 2-*Methylthio*-9-*methyladenine*.—The purine [0·5 g., prepared by method (a) above] was dissolved in boiling water (200 c.c.) containing acetic acid (3 c.c.); after cooling to 60—65°, barium nitrite (2·5 g.) was added, and the solution maintained at this temperature for 45 mins. A slight excess of ammonia was added, and the solution evaporated to one-third its bulk and cooled. The product which separated was dissolved in dilute hydrochloric acid, and the solution decolourised with charcoal and neutralised to litmus with sodium hydroxide. On adding acetic acid (6 c.c.) to the cooled solution, 6-*hydroxy*-2-*methylthio*-9-*methylpurine* (0·3 g.) crystallised in fine needles, m. p. 332° (decomp.) (Found: C, 42·5; H, 4·25; N, 28·5. $C_7H_8ON_4S$ requires C, 42·9; H, 4·1; N, 28·6%).

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THE UNIVERSITY, MANCHESTER. [*Received, June 7th*, 1943.]

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101. *Experiments on the Synthesis of Purine Nucleosides. Part II. A New and Convenient Synthesis of Adenine.*

By J. BADDILEY, B. LYTHGOE, and A. R. TODD.

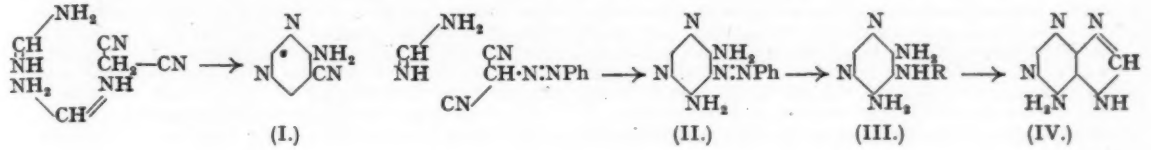
In the course of model experiments, a new synthesis of adenine has been carried out. Formamidine condensed with benzeneazomalononitrile to give 4 : 6-*diamino*-5-*benzeneazopyrimidine*, readily reduced to 4 : 5 : 6-*triaminopyrimidine*. The *thioformyl* derivative of this compound on boiling in aqueous or pyridine solution was converted into adenine. The overall yield of adenine was high. In the course of experiments on other methods for preparing 4 : 5 : 6-triaminopyrimidine, an interesting condensation of formamidine with malononitrile to 4-*amino*-5-*cyanopyrimidine* has been observed.

BEFORE attempting to prepare a 5 : 6-diamino-4-glycosidaminopyrimidine, a necessary intermediate for the synthesis of a 9-glycosidoadenine by the route proposed in the preceding paper, we decided to prepare the parent 4 : 5 : 6-*triaminopyrimidine*, and from it to effect a synthesis of adenine. In his synthesis of adenine, Traube (*Annalen*, 1904, **331**, 64) avoided the difficulty presented by the preparation of this compound by using the more accessible 4 : 5 : 6-triamino-2-thiolpyrimidine; this was converted into 2-thioladenine and desulphurised by treatment with hydrogen peroxide in warm acid solution. The overall yield in this synthesis is poor and as a model for an adenosine synthesis it is of little value, since hydrolysis of the glycosidic linkage would almost certainly occur during desulphurisation. A convenient method for the preparation of pyrimidines unsubstituted in position 2 would therefore be essential for our purposes. Only a few pyrimidines of this type have been described in the literature. They have generally been prepared from the corresponding 2-hydroxypyrimidines by halogenation and reduction (*e.g.*, Angerstein, *Ber.*, 1901, **34**, 3957) or, less frequently, by desulphurisation of 2-thiolpyrimidines by means of hydrogen peroxide (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) or decarboxylation of pyrimidine-2-carboxylic acids (Gabriel and Colman, *Ber.*, 1899, **32**, 1531). Of the aminopyrimidines containing a free 2-position, 4-aminopyrimidine and 4 : 6-diaminopyrimidine have been prepared from 2 : 4 : 6-trichloropyrimidine by Büttner (*Ber.*, 1903, **36**, 2231), but the yields were very low and the method is unsuitable for preparative purposes.

The successful use of formamidine as an intermediate in the synthesis of pyrimidines containing a free 2-position has not hitherto been reported, although alkyl- and aryl-amidines have been widely used in pyrimidine syntheses. Traube (*loc. cit.*) records a failure to isolate any product from the condensation of formamidine with ethyl cyanoacetate. We failed to effect condensation of formamidine with aminomalononitrile, but malononitrile itself condensed readily with formamidine in alcoholic solution. The product, however, was not the expected 4 : 6-diaminopyrimidine, but a substance, $C_5H_4N_4$, identical with the condensation product of thioformamide and aminomethylenemalononitrile (cf. condensation of thioacetamide with aminomethylenemalononitrile in Hoffmann-La Roche, B.P. 546,624). It is therefore 4-*amino*-5-*cyanopyrimidine* (I), formed by condensation of two molecules of formamidine with malononitrile. This mode of reaction is to be attributed to the reactive nature of the methylene group in malononitrile, an intermediate product being presumably aminomethylenemalononitrile. The unusual course of this reaction led us to investigate the reaction between formamidine and other compounds containing a reactive methylene group; the results will be communicated in a separate paper.

The preparation of 4 : 5 : 6-triaminopyrimidine in quantity by nitrosation and reduction of 4 : 6-diaminopyrimidine being dependent on the development of a satisfactory process for synthesising the latter compound, we turned our attention to an alternative route. Formamidine and benzeneazomalononitrile condensed smoothly to give 4 : 6-*diamino*-5-*benzeneazopyrimidine* (II), reduced by hydrogen in presence of Raney nickel to 4 : 5 : 6-tri-

aminopyrimidine (III; R = H). On treatment with aqueous sodium dithioformate (III; R = H) gave 4 : 6-*diamino-5-thioformamidopyrimidine* (III; R = CHS), which on boiling in aqueous or pyridine solution evolved hydrogen sulphide, yielding adenine (IV). The identity of the product was confirmed by direct comparison with adenine from natural sources. Attention is drawn to the fact that the synthesis described gives an overall yield of more than 50% (based on malononitrile), which is a marked improvement on the original Traube method, and makes adenine a readily accessible compound. Similar methods of synthesis could probably be applied in the case of other naturally occurring purines.



(I.) (II.) (III.) (IV.)

Experimental.

Condensation of Formamidine with Malononitrile.—To a solution of formamidine hydrochloride (3·6 g.) and malononitrile (2·0 g.) in absolute alcohol (90 c.c.), alcoholic sodium ethoxide (1·02 g. of sodium in 30 c.c. of absolute alcohol) was added, and the mixture, which evolved ammonia, left at room temperature for 24 hours. The precipitate was collected, washed with cold water to remove sodium chloride, and dried; a further quantity of the same product separated on concentration of the alcoholic mother-liquor. The combined product was sublimed in a vacuum, colourless needles of 4-*amino-5-cyanopyrimidine* (I), m. p. 250°, being obtained (yield, 45%) (Found: C, 50·0; H, 3·4; N, 46·0. $C_5H_4N_4$ requires C, 50·0; H, 3·3; N, 46·4%). The substance was soluble in hot water or dilute hydrochloric acid, but sparingly so in cold water or alcohol; its aqueous solution was neutral to litmus. The *picrate* crystallised from water in yellow needles, m. p. 189° (Found: C, 38·7; H, 2·6; N, 27·3. $C_5H_4N_4,C_6H_3O_7N_3$ requires C, 38·0; H, 2·0; N, 28·0%). Acetylation of 4-amino-5-cyanopyrimidine (0·5 g.) with boiling acetic anhydride for 15 minutes, followed by evaporation in a vacuum and crystallisation from alcohol gave colourless needles (0·5 g.), m. p. 124—125°, soluble in water and alcohol (Found: C, 51·9; H, 3·7. $C_7H_6ON_4$ requires C, 52·0; H, 3·7%). On acetylation of 4-amino-5-cyano-2-methylpyrimidine the expected 4-acetamido-compound is not obtained, the pyrimidine ring opening to give acetyl-acetamidinomethylenemalononitrile (unpublished observations of Dr. F. Bergel), and we therefore consider our substance, which resembles the latter in properties, to be *acetylformamidinomethylenemalononitrile.*

4-Amino-5-cyanopyrimidine was also obtained by refluxing aminomethylenemalononitrile (0·93 g.), alcoholic sodium ethoxide (0·23 g. of sodium in 10 c.c. of alcohol), and thioformamide (0·61 g.) for ½ hour. The product (0·4 g.) which separated on cooling was collected; it had m. p. 250°, undepressed on admixture with the product from formamidine and malononitrile. (This experiment was carried out by Mr. G. W. Kenner.)

4 : 6-*Diamino-5-benzeneazopyrimidine* (II).—Alcoholic sodium ethoxide (1·25 g. of sodium in 20 c.c. of absolute alcohol) was added to a solution of benzeneazomalononitrile (6·1 g.) (Hantzsch and Thompson, *Ber.*, 1905, **38**, 2266) and formamidine hydrochloride (4·3 g.) in absolute alcohol (80 c.c.), and the mixture kept for 1 hour at room temperature and then refluxed for ¼ hour. After dilution with water (300 c.c.) the red solid was collected and recrystallised from alcohol–pyridine (3 : 1). 4 : 6-*Diamino-5-benzeneazopyrimidine* separated in red-brown plates, m. p. 282—286° (decomp.). Yield, 75% (Found: C, 56·2; H, 4·5. $C_{10}H_{10}N_6$ requires C, 56·1; H, 4·7%).

4 : 5 : 6-*Triaminopyrimidine* (III; R = H).—The above azo-compound (2 g.) was dissolved in alcohol (800 c.c.) and hydrogenated (6 hours) at 100°/60 atms. in presence of Raney nickel (0·5 g.). The pale brown solution was filtered from catalyst and evaporated under reduced pressure, and the residue, freed from aniline by washing with ether, recrystallised from alcohol. 4 : 5 : 6-*Triaminopyrimidine* was thus obtained in colourless needles, m. p. 257°. Yield, 90% (Found: C, 38·6; H, 5·8; N, 55·4. $C_4H_7N_5$ requires C, 38·5; H, 5·6; N, 55·9%). The triamine was soluble in cold water and alcohol; aqueous solutions were alkaline to litmus. In one experiment the triamine was accompanied by a small amount of a less soluble substance which separated from the alcoholic reduction solution in yellow plates, m. p. 258° (Found: C, 57·6; H, 4·8; N, 36·6%); it has not yet been further investigated.

4 : 6-*Diamino-5-thioformamidopyrimidine* (III; R = CHS).—The above triamine (1 g.) was dissolved in the minimum quantity of cold water, and sodium dithioformate (2 g.) added. After 12 hours the *thioformyl* derivative was collected and recrystallised from hot water, forming colourless needles (1 g.) which had no m. p. but evolved hydrogen sulphide rapidly above 200° (Found: C, 35·9; H, 4·4; N, 41·0; S, 18·6. $C_5H_7N_5S$ requires C, 35·5; H, 4·1; N, 41·5; S, 18·9%).

Adenine (IV).—The thioformamido-compound (III; R = CHS) (1·0 g.) was suspended in water (20 c.c.), and the mixture refluxed for 12 hours. Hydrogen sulphide was evolved and the solid dissolved completely. On cooling, adenine separated in long colourless needles, m. p. 360° (yield, almost quantitative) (Found for material dried in a vacuum at 110°: C, 44·6; H, 4·0; N, 51·2. Calc. for $C_5H_5N_5$: C, 44·5; H, 3·7; N, 51·9%). The product showed the dimorphism described for adenine by Kossel (*Z. physiol. Chem.*, 1896, **20**, 253) and gave the characteristic colour in Kossel's test (*ibid.*, 1888, **12**, 252). The picrate, silky yellow needles, had m. p. 292°, undepressed by authentic adenine picrate (m. p. 292°). Comparison of the ultraviolet absorption spectrum of the synthetic product with that of authentic natural adenine showed no divergence [maximum at 2630 A. (ε 16,700) in N/20-hydrochloric acid and 2680 A. (ε 15,400) in N/100-sodium hydroxide]. The conversion of (III; R = CHS) into adenine is accomplished more rapidly by using pyridine or quinoline in place of water as a solvent.

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The University, Manchester. [*Received, June 7th*, 1943.]

102. *Some Reactions of Amidines with Derivatives of Malonic Acid.*

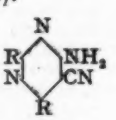
By G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham.

Following an observation that formamidine and malononitrile condense to give 4-amino-5-cyanopyrimidine, the reactions of amidines with several derivatives of malonic acid have been investigated, formamidine, acetamidine, benzamidine, and α-furylamidine being used as representative amidines. With malononitrile, derivatives of 4-amino-5-cyanopyrimidine are invariably produced, the aminomethylene- or substituted aminomethylene-malononitrile presumably acting as an intermediate in the reaction. Production of aminomethylene- or substituted aminomethylene-derivatives also takes place with ethyl cyanoacetate, although here normal condensation to give derivatives of 4-amino-6-hydroxypyrimidine is also possible. Condensation of formamidine and ethyl cyanoacetate in presence of sodium ethoxide gives, according to conditions, ethyl methenylbiscyanoacetate and a compound, $C_9H_9O_3N_3$, provisionally regarded as a pyridine derivative. A possible mechanism for the formation of these compounds is suggested. With ethyl malonate, amidines condense normally in each case to give derivatives of 4 : 6-dihydroxypyrimidine; production of aminomethylene compounds does not occur.

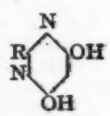
Baddiley, Lythgoe, and Todd (preceding paper) have reported that condensation of formamidine with malononitrile yielded 4-amino-5-cyanopyrimidine (I; R = H) instead of 4 : 6-diaminopyrimidine, which would have been expected by analogy with the condensation of guanidine with malononitrile (Traube, *Annalen*, 1904, **331**, 64). No other cases of the condensation of amidines with malononitrile have hitherto been recorded, and the unexpected course of the formamidine condensation led us to investigate the behaviour of this and other amidines with various derivatives of malonic acid.

With ethyl malonate all the amidines investigated condensed normally, giving derivatives of 4 : 6-*dihydroxypyrimidine* (II; R = H). Formamidine gave (II; R = H), and α-furylamidine 4 : 6-*dihydroxy*-2-α-*furylpyrimidine* (II; R = C_4H_3O). Acetamidine and benzamidine are already known to yield respectively (II; R = Me) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and (II; R = Ph) (Pinner, *Ber.*, 1908, **41**, 3517).

In common with formamidine other amidines reacted abnormally with malononitrile, giving derivatives of (I; R = H); acetamidine gave 4-amino-5-cyano-2 : 6-dimethylpyrimidine (I; R = Me) and benzamidine 4-*amino*-5-*cyano*-2 : 6-*diphenylpyrimidine* (I; R = Ph). α-Furylamidine, however, gave β-(α-*furyl*)-β-*aminomethylenemalononitrile* (III; R = C_4H_3O). In the production of compounds of type (I) those of type (III) are almost certainly intermediates; similar compounds are formed by the interaction of *NN'*-disubstituted formamidines with compounds containing a reactive methylene group (Dains, *Ber.*, 1902, **35**, 2496). For example, *NN'*-diphenylformamidine reacts with ethyl malonate to give ethyl anilinomethylenemalonate and aniline, which react further to produce a monoanilide (IV); secondary condensation to a pyrimidine derivative is impossible in this case. Except in the case of a α-furylamidine we were unable to isolate the hypothetical intermediates (III), presumably because they react too rapidly with a second molecule of amidine. We have shown that formamidine and aminomethylenemalononitrile (III; R = H) condense rapidly, producing (I; R = H). Again, on refluxing in alcoholic solution, α-furylamidine condenses with β-(α-furyl)-β-aminomethylenemalononitrile (III; R = C_4H_3O), giving 4-*amino*-5-*cyano*-2 : 6-*di*-α-*furylpyrimidine* (I; R = C_4H_3O). It may be noted in passing that acetiminoether reacts with aminomethylene derivatives of type (III) to give pyrimidines (Hromatka, D.R.-P. 667,990). Where formation of a compound of type (III) is prevented by substitution in the methylene group of malononitrile, condensation with an amidine proceeds normally; *e.g.*, benzeneazomalononitrile and formamidine yield 4 : 6-diamino-5-benzeneazopyrimidine (Baddiley, Lythgoe, and Todd, *loc. cit.*).

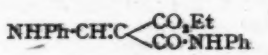


(I.)



(II.)

$NH_2{\cdot}CR{:}C(CN)_2$ (III.)



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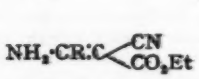

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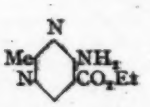
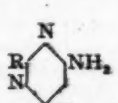


(VI.)

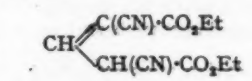


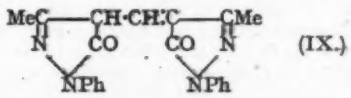
(VII.)

Further support for the hypothesis that compounds of type (III) act as intermediates in the abnormal condensations with malononitrile is found in the reactions of ethyl cyanoacetate with amidines. Contrary to Traube (*loc. cit.*), who records a failure to isolate any product from the reaction of formamidine with ethyl cyanoacetate, we obtained ethyl aminomethylenecyanoacetate (V; R = H) in good yield; (V; R = H) did not undergo further condensation with formamidine, but it reacted readily with thioacetamide in presence of sodium ethoxide, giving ethyl 4-amino-2-methylpyrimidine-5-carboxylate (VI), identified by comparison with an authentic specimen. Traube (*Centr.*, 1902, II, 1229) obtained 4-amino-6-hydroxy-2-methylpyrimidine (VII; R = Me) from ethyl potassiocyanoacetate and acetamidine. In the course of some other work Mr. L. C. Payman in this laboratory has shown that use of the free ester instead of the alkali metal derivative gives the *aminomethylene* derivative (V; R = Me). It may be observed that the substance isolated by Földi, von Fodor,

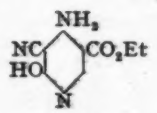
Demjén, Szekeres, and Halmos (*Ber.*, 1942, **75**, 755) as a by-product in the reaction between acetamidine and carbethoxyacetiminoether is almost certainly impure (V; R = Me). When benzamidine is condensed with ethyl cyanoacetate in alcoholic solution, 4-amino-6-hydroxy-2-phenylpyrimidine (VII; R = Ph) and ethyl β-amino-α-cyano-β-phenylacrylate (V; R = Ph) are produced simultaneously in approximately equal amounts; in presence of sodium ethoxide (VII; R = Ph) is the main product (Traube and Herrmann, *Ber.*, 1904, **37**, 2267). As with malononitrile, substitution of the methylene group in ethyl cyanoacetate prevents the occurrence of abnormal reaction; thus ethyl cyanosuccinate and acetamidine yield ethyl 4-amino-6-hydroxy-2-methylpyrimidine-5-acetate (Andersag and Westphal, D.R.-P., 671,787). The results obtained in the above reactions with ethyl cyanoacetate indicate that use of a more stable amidine (*e.g.*, benzamidine) or presence of an alkali-metal ethoxide favours normal condensation to a pyrimidine of type (VII), whereas absence of a condensing agent or a highly reactive amidine (*e.g.*, formamidine) favours production of an aminomethylene derivative (V). As might be expected on general grounds, acetamidine occupies a position intermediate between formamidine and benzamidine in such reactions.

The reaction of formamidine with ethyl cyanoacetate in presence of sodium ethoxide gave rise to two further compounds. One of these, obtained with 0·5 mol. of sodium ethoxide, was identified as ethyl methenylbiscyanoacetate (VIII); its formation is analogous to that of the methenylbispyrazolone derivative (IX) recorded by Dains and Brown (*J. Amer. Chem. Soc.*, 1909, **31**, 1148). The second, obtained when the reaction was carried out in presence of 1·5 mols. of sodium ethoxide, was a *substance*, $C_9H_9O_3N_3$, which we regard provisionally as a pyridine derivative, possibly (X), although a final decision has not been reached. The formation of ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate on warming (VIII) with alcohol has been recorded by Dimroth (*Ber.*, 1902, **35**, 2882). A compound (X) could arise by a condensation involving two molecules of ethyl cyanoacetate to produce the amide (XI), followed by cyclisation of the latter after the manner of a Thorpe reaction. Our view that the substance $C_9H_9O_3N_3$ is a pyridine derivative of the type indicated finds additional support in the similarity of its absorption spectrum to that of ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate. In this connection it may be mentioned that interaction of formamidine and ethyl acetoacetate in presence of sodium ethoxide gives rise to a *compound*, m. p. 79—80°, which we regard provisionally as (XII) and which is analogous to the hypothetical amide (XI). From this reaction Pinner (*Ber.*, 1886, **18**, 2846) obtained a substance, m. p. 73°, which he described on very scanty evidence as ethyl β-cyanocrotonate; we were unable to obtain any compound having this composition and we are of the opinion that Pinner's product was simply a rather impure specimen of the product we believe to be (XII). The compound, m. p. 79—80°, has the composition required by structure (XII) and on catalytic hydrogenation absorbs 3 mols. of hydrogen, but rigid proof of constitution has not yet been obtained.

(VIII.) 



(IX.)



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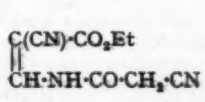
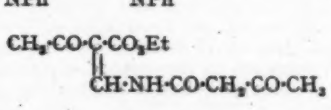


(XI.)



(XII.)

Arising from the investigations above reported, a few of the condensations described were carried out, formiminoether being substituted for formamidine. As expected, similar products were obtained, although the yields were usually lower. With ethyl cyanoacetate, formiminoether condensed to give the aminomethylene derivative (V; R = H); when carried out in presence of sodium ethoxide, the main product was ethyl methenylbiscyanoacetate, although small amounts of (V; R = H) were also formed. With malononitrile, a small amount of 4-amino-5-cyanopyrimidine was formed, and with ethyl acetoacetate ethyl aminomethyleneacetoacetate was produced in low yield together with traces of a compound, m. p. 201°, which was not further investigated.

Experimental.

1. *Condensations with Ethyl Malonate.*—*4 : 6-Dihydroxypyrimidine* (II; R = H). Formamidine hydrochloride (80·5 g.) was added to ice-cold alcoholic sodium ethoxide (69 g. = 3 atoms of sodium in 1 l. of alcohol), followed, after filtration from sodium chloride, by ethyl malonate (160 g.), and the mixture was kept overnight. The solid which separated was collected, dissolved in water, and the solution acidified with hydrochloric acid. The precipitated *4 : 6-dihydroxypyrimidine* was recrystallised from hot water (yield, 80%). It was practically insoluble in organic solvents and on heating decomposed above 230° (Found: C, 42·2; H, 3·6; N, 25·6. $C_4H_4O_2N_2$ requires C, 42·8; H, 3·6; N, 25·0%).

4 : 6-Dihydroxy-2-α-furylpyrimidine (II; R = C_4H_3O). α-Furylamidine hydrochloride (1·46 g.) (Pinner, *Ber.*, 1892, **25**, 1416), alcoholic sodium ethoxide (0·69 g. = 3 atoms of sodium in 10 c.c. of alcohol), and ethyl malonate (1·6 g.) were refluxed for 2 hours, and the product left overnight and then worked up as above. The *pyrimidine* (yield, 42%) separated from water in colourless needles which decomposed above 290° (Found: C, 53·8; H, 3·5; N, 15·1. $C_8H_6O_3N_2$ requires C, 53·9; H, 3·4; N, 15·7%).

2. *Condensations with Malononitrile.*—*4-Amino-5-cyano-2 : 6-dimethylpyrimidine* (I; R = Me). Acetamidine hydrochloride (9·45 g.), alcoholic sodium ethoxide (2·3 g. = 1 atom of sodium in 50 c.c. of alcohol), and malononitrile (6·6 g.) were refluxed together for 3 hours. After cooling, the precipitate was collected, washed free from salt with cold water, and recrystallised from alcohol. 4-Amino-5-cyano-2 : 6-dimethylpyrimidine was obtained in colourless plates,

m. p. 218° (yield, 50%) (Found : C, 56·2; H, 4·8; N, 38·2. Calc. for $C_7H_8N_4$: C, 56·9; H, 5·4; N, 37·8%). Huber and Hölscher, (*Ber.*, 1938, **71**, 87), who prepared this compound by a different route, give m. p. 220·5°.

4-*Amino*-5-*cyano*-2 : 6-*diphenylpyrimidine* (I; R = Ph), prepared in similar fashion from benzamidine and malononitrile, crystallised from ethyl acetate in colourless needles, m. p. 211° (yield, 45%) (Found : C, 75·1; H, 4·4; N, 20·1. $C_{17}H_{12}N_4$ requires C, 75·0; H, 4·4; N, 20·6%).

β-(α-Furyl)-β-aminomethylenemalononitrile (IV; R = C_4H_3O). When an alcoholic solution of α-furylamidine (from 3·3 g. of the hydrochloride) and malononitrile (1·32 g.) was kept overnight, colourless needles separated; recrystallised from water, the *compound* had m. p. 182° (yield, 30%) (Found : C, 60·3; H, 3·4; N, 26·7. $C_8H_5ON_3$ requires C, 60·4; H, 3·1; N, 26·4%). The same compound was obtained (yield, 17%) when α-furyliminoether was substituted for α-furylamidine in the condensation.

4-*Amino*-5-*cyano*-2 : 6-*di-α-furylpyrimidine* (I; R = C_4H_3O). The above compound (IV; R = C_4H_3O) (0·8 g.), α-furylamidine hydrochloride (0·65 g.), and alcoholic sodium ethoxide (from 0·115 g. ≡ 1 atom of sodium in 25 c.c. of alcohol) were refluxed for 8 hrs. The solid which separated was freed from salt by washing with water and recrystallised from ethyl acetate, forming colourless needles, m. p. 245—246° (Found : C, 61·6; H, 3·2; N, 22·0. $C_{13}H_8O_2N_4$ requires C, 61·9; H, 3·2; N, 22·2%).

Condensation of formamidine with aminomethylenemalononitrile. Aminomethylenemalononitrile (1·85 g.) (Passalacqua, *Gazzetta*, 1913, **43**, II, 566) was added to an alcoholic solution of formamidine (from 1·6 g. of the hydrochloride) at room temperature. After 30 mins. the precipitated solid was collected and recrystallised from alcohol. The product (yield, 42%) had m. p. 249°, undepressed by 4-amino-5-cyanopyrimidine (m. p. 250°; Baddiley, Lythgoe, and Todd, *loc. cit.*).

3. *Condensations of Formamidine with Ethyl Cyanoacetate.*—(a) *Ethyl aminomethylenecyanoacetate* (V; R = H). Formamidine hydrochloride (4 g.), alcoholic sodium ethoxide (1·15 g. ≡ 1 atom of sodium in 35 c.c. of alcohol), and ethyl cyanoacetate (2·5 g.) were refluxed together for 5 hrs., and the solution filtered from sodium chloride, evaporated to small bulk, and diluted with water. The ethyl aminomethylenecyanoacetate which separated crystallised from ethyl acetate in needles, m. p. 140° (yield, 80%) (Found : C, 51·2; H, 6·0; N, 19·7. Calc. for $C_6H_8O_2N_2$: C, 51·5; H, 5·8; N, 20·0%). De Bollemont (*Bull. Soc. chim.*, 1901, **25**, 41) gives m. p. 130°.

The above aminomethylene derivative (1·2 g.) was refluxed for 30 mins. with thioacetamide (0·63 g.) and alcoholic sodium ethoxide (0·19 g. ≡ 1 atom of sodium in 10 c.c. of alcohol), and the solution evaporated to small bulk. Ethyl acetate was added, sodium hydrogen sulphide removed, and the filtrate evaporated. The viscous residue on trituration with water yielded a quantity of white solid. Recrystallised from alcohol, this formed needles, m. p. 119—120°, undepressed by authentic ethyl 4-amino-2-methylpyrimidine-5-carboxylate (m. p. 120°; Todd and Bergel, J., 1937, 364).

(b) *Ethyl methenylbiscyanoacetate* (VIII). Formamidine hydrochloride (12 g.), ethyl cyanoacetate (16·8 g.), and alcoholic sodium ethoxide (5·1 g. ≡ 1·5 atoms of sodium in 75 c.c. of alcohol) were refluxed for 5 hours, the mixture evaporated to dryness, and the residue (sodium salt) dissolved in water. On acidification ethyl methenylbiscyanoacetate separated; recrystallised from dioxan (yield, 60%), it had m. p. 187° (decomp.), undepressed by an authentic specimen prepared according to Ruhemann and Browning (J., 1898, **73**, 282) (Found : N, 12·0. Calc. for $C_{11}H_{12}O_4N_2$: N, 11·9%). Light absorption in alcohol : Maxima at 2255 A. (ε, 10,700), 2735 A. (ε, 9,400), and 3560 A. (ε, 35,000).

(c) *Compound* $C_9H_9O_3N_3$. Formamidine hydrochloride (4 g.) was added to cold alcoholic sodium ethoxide (2·87 g. ≡ 2·5 atoms of sodium in 60 c.c. of alcohol), and the solution filtered from sodium chloride. After addition of ethyl cyanoacetate (5·6 g.) and keeping for 4 hours the precipitate was collected, dissolved in water, and the solution acidified. The *product* which separated crystallised from hot water in colourless needles (1·2 g.), m. p. 280—281° (decomp.) (Found : C, 51·9; H, 4·3; N, 19·8. $C_9H_9O_3N_3$ requires C, 52·2; H, 4·3; N, 20·3%). Light absorption in alcohol : Maxima at 2730 A. (ε, 23,000) and 3370 A. (ε, 28,000). Ethyl 2 : 6-dihydroxypyridine-3 : 5-dicarboxylate (Dimroth, *loc. cit.*) showed maxima at 2690 A. (ε, 19,700) and 3260 A. (ε, 18,500) in alcoholic solution.

4. *Condensation of Benzamidine with Ethyl Cyanoacetate.*—An alcoholic solution of benzamidine (from 3·12 g. of the hydrochloride) was refluxed with ethyl cyanoacetate (2·26 g.) for 8 hours. After the solvent had been evaporated and water (20 c.c.) added, the crystalline solid was collected and extracted with hot water. Crystallisation of the residue from alcohol gave ethyl β-amino-α-cyano-β-phenylacrylate (V; R = Ph), m. p. 123—124°, undepressed by a specimen (m. p. 125°) prepared by the method of Atkinson, Ingham, and Thorpe (J., 1907, **91**, 590) (yield, 28%). The hot aqueous extract on cooling deposited 4-amino-6-hydroxy-2-phenylpyrimidine (yield, 21%), m. p. 252° (Traube and Herrmann, *loc. cit.*, give m. p. 252°). When, in the above condensation, benzamidine was replaced by benziminoether, the only product identified was ethyl β-amino-α-cyano-β-phenylacrylate (yield, 8%).

5. *Condensation of Formamidine with Ethyl Acetoacetate.*—Formamidine hydrochloride (8 g.) and cold alcoholic sodium ethoxide (4·6 g. ≡ 2 atoms of sodium in 100 c.c. of alcohol) were mixed and filtered from sodium chloride; ethyl acetoacetate (26 g.) was added, and the mixture left for 2 hours. The precipitate was collected, dissolved in water, and the solution acidified. The *compound* which separated crystallised from light petroleum (b. p. 40—60°) in colourless needles (14·5 g.), m. p. 78—79° (Found : C, 54·8; H, 6·4; N, 5·8. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·4; N, 5·6%). Microhydrogenation (PtO_2) : 30·6 mg. absorbed 9·94 c.c. of hydrogen at 14° and 733 mm., corresponding to 3·2 mols. of hydrogen. Attempts to obtain this substance by condensation of ethyl acetoacetate with ethyl aminomethylenecyanoacetate were unsuccessful.

6. *Condensations using Formiminoether in Place of Formamidine.*—(a) *With malononitrile.* Formiminoether (from 5·5 g. of the hydrochloride) and malononitrile (1·65 g.), kept in alcoholic solution (50 c.c.) for 12 hours and worked up in the usual way, gave a small amount (0·15 g.) of 4-amino-5-cyanopyrimidine, m. p. 250°.

(b) *With ethyl cyanoacetate.* In absence of sodium ethoxide formiminoether and ethyl cyanoacetate, refluxed in alcoholic solution for 4—5 hours, gave ethyl aminomethylenecyanoacetate (yield, 63%). In presence of sodium ethoxide ethyl methenylbiscyanoacetate was produced (yield, *ca.* 50%) together with a small amount of ethyl aminomethylenecyanoacetate; no evidence of the formation of the compound $C_9H_9O_3N_3$ was obtained.

(c) *With ethyl acetoacetate.* Formiminoether (from 5·5 g. of the hydrochloride) and ethyl acetoacetate (6·5 g.) in absolute alcohol (20 c.c.) were left at room temperature for 2 days, and the solution evaporated. The residue was extracted first with light petroleum (b. p. 40—60°) and then with ether. After concentration of the ethereal extract a very small amount of solid, m. p. 201°, separated. Further concentration yielded ethyl aminomethyleneacetoacetate, m. p. 43—45°, undepressed by an authentic specimen.

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103. *The Influence of the 6-Nitro-group on the Halogenation, Nitration, Mercuration, and Diazo-coupling of 6-Nitro-1-naphthylamine and of Some Related Naphthalides.*

By Herbert H. Hodgson and Harold S. Turner.

The 6-nitro-group favours halogenation, nitration, mercuration, and diazo-coupling at the 4-position in 6-nitro-1-naphthylamine and related naphthalides.

In many of the reactions of 6-nitro-1-naphthylamine, *e.g.*, bromination, nitration, mercuration, and diazo-coupling, the 4-position is found to be so much more reactive than the 2-position, that monosubstitution by electrophilic (kationoid) reagents occurs in that position exclusively. These results are in accord with the deductions of Robinson and Thompson (J., 1932, 2015; cf. also Bell, *ibid.*, p. 2732) which indicate that electronic effects (in this case inhibiting effects) are readily transmitted from the 6- to the 2- rather than to the 4-position, whereas the nitration of 1-nitro-*p*-toluenesulphon-2-naphthalide in the 6-position is an example of an activating effect. In this respect, therefore, 6-nitro- differs from the isomeric 5-nitro-1-naphthylamine, whose reactivity in the 2-position towards some electrophilic reagents other than nitric acid is probably due to the inhibiting effect on the 4-position of the kationoid nitro-group in the 5-position (Hodgson and Turner, J., 1942, 723).

The nitration of 5-nitroaceto-1-naphthalide in the 4-position must be regarded as anomalous and analogous to the predominant 8-nitration of nitronaphthalene itself (Hodgson, *J. Soc. Dyers Col.*, 1936, **52**, 369), whereas the nitration of 6-nitroaceto-1-naphthalide gives a mixture of 2 : 6- and 4 : 6-dinitroaceto-1-naphthalides in the ratio of *ca.* 1 : 5, determined as described on p. 393.

Like the 5-nitro-isomeride, 6-nitroaceto-1-naphthalide is chlorinated simultaneously in the 2- and the 4-position, monochlorination not being detectable, but 6-nitro-1-naphthylamine, unlike its 5-isomeride, is monobrominated exclusively in the 4-position. The authenticity of 4-*bromo*-6-*nitro*-1-*naphthylamine* was established by its conversion into 1 : 4-*dibromo*-6-*nitronaphthalene*, which in turn was oriented by its difference from the only possible alternative, 1 : 2-*dibromo*-6-*nitronaphthalene*, prepared from 1-*bromo*-6-*nitro*-p-*toluenesulphon*-2-*naphthalide* by hydrolysis, diazotisation of the amine produced, and introduction of bromine by the Sandmeyer reaction. The 1-bromo-compound was prepared by nitration of 1-bromo-*p*-toluenesulphon-2-naphthalide, made according to Consden and Kenyon (J., 1935, 1595), and that the nitro-group entered the 6-position was confirmed by hydrolysis to the amine and deamination to form 1-*bromo*-6-*nitronaphthalene*.

4-*Bromo*-6-*nitro*-1-*naphthylamine* was deaminated to give 8-*bromo*-2-*nitronaphthalene*, which was different from the monobromonitronaphthalene prepared but not identified by Braun, Hahn, and Seemann (*Ber.*, 1922, **55**, 1697) by monobromination of 2-nitronaphthalene, but now identified as 5-bromo-2-nitronaphthalene, since it is identical with the product obtained by replacement of the amino-group in 6-nitro-1-naphthylamine by bromine (Sandmeyer reaction).

Like its 5-nitro-isomeride (Hodgson and Turner, *loc. cit.*), 6-*nitro*-p-*toluenesulphon*-1-*naphthalide* is nitrated simultaneously at the 2- and the 4-position, even with nitric acid in amount insufficient for mononitration, and the 2 : 4 : 6-*trinitro*-compound is hydrolysed to 2 : 4 : 6-*trinitro*-1-*naphthylamine*.

The 4-mercuration of 6-nitro-1-naphthylamine was established by conversion of the 6-*nitro*-1-*naphthylamine*-4-*mercuriacetate* into 1-*bromo*-4-*iodo*-6-*nitronaphthalene*, which was different from an authentic specimen of the 2-*iodo*-analogue prepared from 1-*bromo*-6-*nitro*-p-*toluenesulphon*-2-*naphthalide* by hydrolysis and replacement of the amino-group by iodine.

Finally, diazotised *p*-toluidine coupled with 6-nitro-1-naphthylamine in the 4-position, as shown by the formation of a stable hydrochloride and by ready diazotisation of the amino-group and subsequent coupling of the diazonium compound with resorcinol, an ease of reactivity unknown in *o*-aminoazo-compounds.

Experimental.

All m. p.'s are corrected.

6-Nitro-1-naphthylamine was prepared according to Hodgson and Turner (this vol., p. 318). Its *picrate* crystallised from ethyl alcohol in pale yellow prisms, m. p. 197° (Found : N, 17·1. $C_{10}H_8O_2N_2,C_6H_3O_7N_3$ requires N, 16·8%).

Acylation of 6-*Nitro*-1-*naphthylamine.*—6-*Nitroformo*-1-*naphthalide*, from the amine and formic acid, crystallised from methyl alcohol (charcoal) in cream needles, m. p. 193° (Found : N, 12·65. $C_{11}H_8O_3N_2$ requires N, 12·95%).

6-*Nitro*-p-*toluenesulphon*-1-*naphthalide* was obtained by grinding the nitro-amine (1·5 g.) with *p*-toluenesulphonyl chloride (2·0 g.), and heating the mixture on the water-bath for 1½ hrs. with acetone (7 c.c.) and water (30 c.c.), sodium carbonate being added as required. The solid was filtered off, washed with water, extracted with hot 4% aqueous sodium hydroxide (175 c.c.), and the filtered extract treated with carbon dioxide to give the naphthalide (2·15 g.), which crystallised from ethyl alcohol in slender, colourless needles, m. p. 205·5° (Found : N, 8·6. $C_{17}H_{14}O_4N_2S$ requires N, 8·55%). The insoluble residue from the extraction was 6-*nitrodi*-p-*toluenesulphon*-1-*naphthalide*, which crystallised from acetone in colourless prisms, m. p. 204·5—205·5° (sinters at 192°) (Found : N, 5·8. $C_{24}H_{20}O_6N_2S_2$ requires N, 5·65%).

6-*Nitronaphthyl*-1-*maleamic acid*. A solution of 6-nitro-1-naphthylamine (1·0 g.) and maleic anhydride (0·6 g.) in chloroform (15 c.c.) was boiled for ½ min., a trace of tar removed, and the filtrate allowed to cool; the resulting yellow 6-*nitronaphthyl*-1-*maleamic acid* (0·7 g.) crystallised from ethyl acetate–ethylene dichloride (equal vols.) in cream microneedles, m. p. 181° (Found : N, 9·6. $C_{14}H_{10}O_5N_2$ requires N, 9·8%), readily soluble in alkalis and reprecipitated by acids.

Replacement of the Amino-group by Halogen.—1-*Chloro*-6-*nitronaphthalene*. A solution of 6-nitro-1-naphthylamine (1·0 g.) in glacial acetic acid (10 c.c.) was stirred below 20° into one of sodium nitrite (0·6 g.) in sulphuric acid (5 c.c., *d* 1·84), the mixture kept for 15 mins., and then poured into a cold solution of cuprous chloride (3 g.) in hydrochloric acid (30 c.c., *d* 1·16); after an hour, the mixture was diluted with water, the precipitate filtered off, dried, and extracted

with acetone, and the decolorised (charcoal) extract evaporated to 5 c.c., and treated with ice. The crystalline precipitate of 1-*chloro*-6-*nitronaphthalene*, recrystallised from aqueous methyl alcohol and then from aqueous ethyl alcohol, formed cream needles, m. p. 118—120° (Found: N, 6·8. $C_{10}H_6O_2NCl$ requires N, 6·7%).

1-*Bromo*-6-*nitronaphthalene* was obtained when 6-nitro-1-naphthylamine (1·0 g.) was ground with a mixture of hydrobromic acid (5 c.c., 60%), ice and water (40 g.), the resulting hydrobromide being diazotised by addition of sodium nitrite (0·7 g. in 5 c.c. of water) below 10°. The filtered solution of the diazonium salt was added to a solution of cuprous bromide (5 g.) in hydrobromic acid (60 c.c., 20%) at 60°; nitrogen was evolved during ½ hr., and the precipitate of 1-bromo-6-nitronaphthalene was then removed and crystallised first from acetone and then from aqueous acetone (charcoal), being obtained in very pale yellow (almost colourless) needles, m. p. 130·5—131° (Found: N, 5·75. $C_{10}H_6O_2NBr$ requires N, 5·55%).

1-*Iodo*-6-*nitronaphthalene* was formed when a solution of the nitroamine (1·0 g.) in hydrochloric acid (4 c.c., *d* 1·16) and water (25 c.c.) was diazotised (1·0 g.) at 0—5° with sodium nitrite (0·7 g. in 5 c.c. of water), and the solution of the diazonium salt filtered and treated with one of potassium iodide (5 g.) in the minimum quantity of water. After ½ hr. the black precipitate was removed and refluxed with ethyl alcohol (35 c.c.) and charcoal; the liquid was filtered hot, and on cooling, 1-iodo-6-nitronaphthalene was deposited in colourless needles, which were recrystallised from ethyl alcohol–acetone (9 : 1); m. p. 73° (Found: I, 42·1. $C_{10}H_6O_2NI$ requires I, 42·3%).

Chlorination of 6-*Nitroaceto*-1-*naphthalide*. A solution of 6-nitro-1-naphthylamine (3·0 g.) in glacial acetic acid (25 c.c.) was boiled with acetic anhydride (4 c.c.) for 10 mins., and the filtered solution treated with chlorine at 90° under reflux for ¼ hr. After being evaporated to 20 c.c., the cooled solution deposited (scratching), 2 : 4-*dichloro*-6-*nitroaceto*-1-*naphthalide*, which crystallised from glacial acetic acid in short, cream needles, m. p. 243° (Found: N, 9·6. $C_{12}H_6O_3N_2Cl_2$ requires N, 9·4%). This (1·1 g.) was heated under reflux with sulphuric acid (10 c.c., 50%) and ethyl alcohol (10 c.c.) for 1 hour; the red solution, from which the amine sulphate had already begun to crystallise, was cooled, diluted with water, and the red 2 : 4-*dichloro*-6-*nitro*-1-*naphthylamine* (0·85 g.) was twice crystallised from ethyl alcohol containing 20% of acetone, being obtained in orange-red, felted needles, m. p. 177—178° (Found: N, 11·0. $C_{10}H_6O_2N_2Cl_2$ requires N, 10·9%).

Monobromination of 6-*Nitro*-1-*naphthylamine*.—A solution of the amine (3·0 g.) in dry chloroform (70 c.c.) was vigorously stirred at −5° during the addition of a solution of bromine (0·75 c.c.) in dry chloroform (12·5 c.c.) during 10 mins.; after a further 30 mins.' stirring at −5°, the red-tinted precipitate of 4-bromo-6-nitro-1-naphthylamine hydrobromide (4·0 g.) was filtered off, washed with chloroform and dry ether, dried, and gradually hydrolysed by trituration with very dilute aqueous ammonia. The *base* was washed with water and dried in a vacuum; it crystallised from aqueous ethyl alcohol in red needles, m. p. 123—124° (Found: N, 10·8. $C_{10}H_7O_2N_2Br$ requires N, 10·5%).

1-*Bromo*-7-*nitronaphthalene*.—The foregoing base (2·55 g.), dissolved in glacial acetic acid (35 c.c.), was diazotised by addition below 20° to a solution of sodium nitrite (1·0 g.) in sulphuric acid (20 c.c., *d* 1·84), and added to a well-stirred suspension of finely divided yellow cuprous oxide (4·0 g.) in ethyl alcohol (70 c.c.) (cf. Hodgson and Turner, J., 1942, 748). This mixture was poured into water (600 c.c.) and kept for 2 days for the precipitate to become tangible; this was removed, extracted with acetone, the extract refluxed with norit, filtered, and allowed to crystallise by gradual addition of ice. When twice recrystallised from 90% alcohol containing 5% of acetone, 1-*bromo*-7-*nitronaphthalene* was obtained in cream needles, m. p. 104—105° (Found: N, 5·7. $C_{10}H_6O_2NBr$ requires N, 5·5%).

1 : 4-*Dibromo*-6-*nitronaphthalene*.—4-Bromo-6-nitro-1-naphthylamine (3·1 g.), dissolved in glacial acetic acid (35 c.c.), was diazotised as above, and the solution of the diazonium salt added to a cold solution of cuprous bromide (8·0 g.) in hydrobromic acid (80 c.c., 30%), and left overnight to complete decomposition. On dilution with water, the crude product was precipitated, removed, and extracted with acetone, the extract being decolorised (norit) and allowed to crystallise; 1 : 4-*dibromo*-6-*nitronaphthalene* (1·65 g.) was obtained in cream needles, m. p. 110° (Found: Br, 48·1. $C_{10}H_5O_2NBr_2$ requires Br, 48·4%).

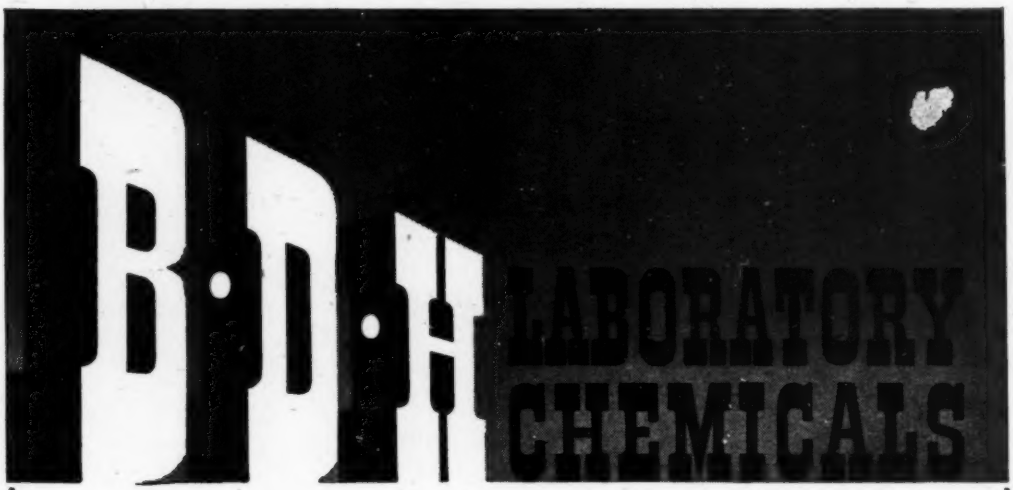
6-*Nitronaphthalene*-1-*azo*-β-*naphthol* was formed when a solution of 6-nitro-1-naphthylamine (1·5 g.) in glacial acetic acid (20 c.c.) was diazotised by addition to a mixture of sodium nitrite (0·8 g.) in sulphuric acid (15 c.c., *d* 1·84) below 20°; after 20 mins. the solution of the diazonium compound was diluted by ice (100 g.), added to one of β-naphthol (1·2 g.) in 20% aqueous sodium hydroxide (165 c.c.) and water (90 c.c.) below 10°, the mixture heated on the water-bath for 15 mins., and the azo-compound (yield, almost theoretical) removed, and crystallised first from hot acetone and then from glacial acetic acid, forming deep red needles, m. p. 220° (Found: N, 12·2. $C_{20}H_{13}O_3N_3$ requires N, 12·2%).

Nitration of 1-*Bromo*-p-*toluenesulphon*-2-*naphthalide*: *Preparation of* 1 : 2-*Dibromo*-6-*nitronaphthalene*.—The naphthalide (5 g.), prepared according to Consden and Kenyon (J., 1935, 1595), was dissolved in glacial acetic acid (25 c.c.), treated at 30—40° with a solution of nitric acid (0·45 c.c., *d* 1·5) in glacial acetic acid (4·5 c.c.), then heated carefully on the water-bath at 50—60° for 15 mins. until crystals of 1-*bromo*-6-*nitro*-p-*toluenesulphon*-2-*naphthalide* appeared; the mixture was then cooled (with scratching) below 10°, and the crystals (2·1 g.) filtered off and washed with glacial acetic acid; they crystallised from acetone in cream prisms, m. p. 197—198° (Found: N, 6·75. $C_{17}H_{13}O_4N_2BrS$ requires N, 6·65%). This compound (3·0 g.) was hydrolysed to the free amine by dissolution in sulphuric acid (8 c.c., *d* 1·84) at 40°, and the solution cooled below 20°; sodium nitrite (0·8 g.) in sulphuric acid (5 c.c., *d* 1·84) was added, and the mixture diazotised by running it into glacial acetic acid (20 c.c.) below 20°. After 15 mins., the diazonium solution was added to one of cuprous bromide (7·5 g.) in hydrobromic acid (60 c.c., 25%), kept overnight, diluted with water (200 c.c.), and filtered; the precipitate was boiled with acetone, the extract cooled, and the resulting crystals of 1 : 2-*dibromo*-6-*nitronaphthalene* recrystallised from methyl alcohol–acetone (1 : 1), forming cream needles, m. p. 175° (Found: Br, 48·1. $C_{10}H_5O_2NBr_2$ requires Br, 48·4%).

Orientation of 1-*Bromo*-6-*nitro*-p-*toluenesulphon*-2-*naphthalide*.—The substance (3 g.) was hydrolysed and diazotised as above, and the solution of the diazonium salt run into a suspension of red cuprous oxide (8·0 g.) in methyl alcohol (40 c.c.); a vigorous evolution of nitrogen occurred, and the temperature rose to 60°. After dilution with water, the precipitate was refluxed with acetone (50 c.c.) for ½ hr., the extract decolorised (charcoal), filtered, evaporated to 8 c.c., and cooled, and the precipitated 1-bromo-6-nitronaphthalene recrystallised from methyl alcohol containing 30% of acetone; it formed long, pale yellow needles, m. p. 129·5° (Found: N, 5·7%), mixed m. p. with authentic sample (see above) 130°; mixed m. p. 105—116° with 1-bromo-3-nitronaphthalene (m. p. 131·5—132·5°) prepared from 3-nitro-1-naphthylamine (cf. Veselý and Chudozilov, *Chem. Listy*, 1925, **19**, 260, who give m. p. 128—129° for 1-bromo-3-nitronaphthalene).

2 : 4-*Dibromo*-6-*nitro*-1-*naphthylamine*.—6-Nitro-1-naphthylamine (0·7 g.) was monobrominated as above (bromine, 0·18 c.c.; chloroform, 11·6 c.c.), the 4-bromo-6-nitro-1-naphthylamine removed, washed, dried, redissolved in chloroform (50 c.c.), and brominated a second time exactly as before. The precipitated 2 : 4-dibromo-6-nitro-1-naphthylamine hydrobromide was removed, basified, and the free *base* crystallised from acetone, forming red, felted needles, m. p. 195° (Found: N, 8·4. $C_{10}H_6O_2N_2Br_2$ requires N, 8·1%).

Nitration of 6-*Nitroaceto*-1-*naphthalide*.—The finely divided substance (3·3 g.) was added gradually (15 mins.) to well-stirred nitric acid (25 c.c., *d* 1·5) below 5°, the stirring continued for 5 mins., the mixture poured on ice, and a small sample, which proved to be a mixture, crystallised from glacial acetic acid; m. p. 183·5° (darkens at 170·5°) (Found: N, 14·8. Calc. for a dinitroacetonaphthalide: N, 15·3%). The remainder of the precipitate (2·0 g.) was refluxed for



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